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Synthesis And Photochemical Properties Of Some Porphyrin Derivatives

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SYNTHESIS AND PHOTOCHEMICAL PROPERTIES OF SOME PORPHYRIN DERIVATIVES

by

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ABSTRACT

The initial step of photosynthesis involves transfer of an electron from a photo-excited porphyrin donor to a nearby ubiquinone acceptor. Compounds containing a porphyrin covalently linked to a benzoquinone have been shown to mimic this initial transfer and as such are useful models for the study of photo-induced intramolecular electron transfer. The first chapter of this thesis describes the synthesis of a linked porphyrin-benzoquinone species, designated P4Q. This compound consists of a tetra-aryl porphyrin linked cis-1,3 across a cyclobutane ring to a benzoquinone.

The photophysical properties of this compound and of two precursor species, the hydroquinone analog and the dimethoxy phenyl analog, designated as $P4QH_2$ and P4DMB respectively, were measured in six solvents. The results indicate that intramolecular photo-induced electron transfer is possible in P4Q, and that relative to similar species it is surprisingly facile. The relatively fast observed rates for this electron transfer are rationalized in terms of the mediating role that the connecting linkage plays. The observed solvent effect on the rate of electron transfer was found to be consistent with Marcus theory.

The second and final chapter of this thesis outlines the attempted preparation of a water soluble porphyrin-

cyclodextrin species and the attempts to determine complex dissociation constants for β-cyclodextrin-electron acceptor complexes in aqueous solution. This was an attempt to extend the use of β-cyclodextrin as a connecting linkage to aqueous solution. Cyclodextrins are useful as connecting linkages due to their ability to form inclusion complexes with a wide variety of species. This allows one porphyrin derivative, that linked to the cyclodextrin, to be used for screening several potential electron acceptors with a minimum of synthetic work. The attempts to measure the equilibrium dissociation constants were part of an attempt to quantify the kinetics of electron transfer in this system.

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation to my supervisor, Dr. Alan Weedon. I thank you for your assistance, your guidance and your wisdom. I would also like to thank you for your continued optimism, even under the most negative circumstances.

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CHAPTER ONE: INTRAMOLECULAR PHOTOINDUCED ELECTRON TRANSFER; THE SYNTHESIS AND ANALYSIS OF A CYCLOBUTANE LINKED PORPHYRIN-BENZOQUINONE SPECIES

(A) INTRODUCTION

Photosynthesis, the process by which green plants convert solar radiation into chemical energy, is among the most efficient systems known for this conversion. The overall efficiency of this process is ca. 16%, which is as good as or better than most commercial silicon based solar cells (1). Clearly, if a synthetic system can be designed to match or exceed the efficiency of photosynthesis, such a system would be of considerable importance.

The photosynthetic reaction centers of green plants and algae are known to operate along two major pathways, termed photosystem one (PSI) and photosystem two (PSII). Both involve the transfer of an electron from a photo-excited chlorophyll donor to a nearby acceptor. The electron acceptor of PSI is not well characterized but is believed to involve an iron-sulfur center. The electron acceptor of PSII has been identified as plastoquinone (1). This is analogous to the reaction center of the photosynthetic bacteria Rhodopseudomonas viridis which has been isolated, crystallized, and subjected to structure determination by X-ray crystallography (2). The reaction center of this bacteria utilizes a dimer of bacteriochlorophyll as the donor and ubiquinone as the electron acceptor.

A number of factors may contribute to the efficiency of photochemical electron transfer in these natural reaction centers. These include: a) the relative energy levels of the

highest occupied molecular orbital (HOMO) of the photo-excited donor and the lowest unoccupied molecular level (LUMO) of the ground state acceptor, b) the relative energy levels of the donor radical cation LUMO and the acceptor radical anion HOMO, c) the distance separating the donor and acceptor, d) the relative orientation of the chromophores of the donor and acceptor, and e) the nature of the media (both formal connecting linkages and solvent) separating the donor and acceptor.

To determine which of, and how, these features contribute to the overall efficiency of the natural reaction centers, it has been found expedient to study purely synthetic models. This approach has the major advantage that it is much easier to systematically modify the components of a synthetic model than it is to modify the natural reaction centers.

In an attempt to limit the number of variables, donor and acceptor species which resemble those found in the natural reaction centers are commonly used. Accordingly, the electron donors chosen have been tetra-aryl or octa-alkyl porphyrins and the acceptors have been substituted quinones.

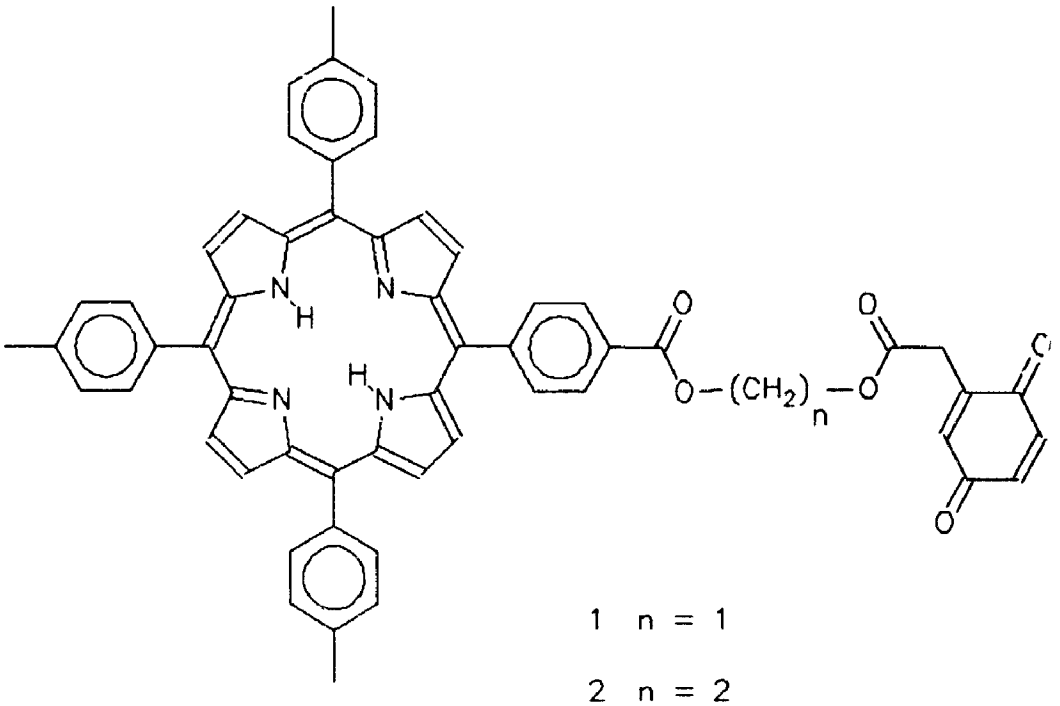
The donor and acceptor used in these model systems are covalently linked to each other, to allow for control of the internuclear distances. The relative geometry of the donor and acceptor in the natural reaction centers is fixed by the protein structures supporting them. The model systems however must rely on the connecting linkage to provide the requisite proximity and orientation. The connecting linkage may also

provide a through-bond pathway for the transfer of an electron from photo-excited donor to acceptor. Therefore the electronic structure of the linkage, as well as its length, shape and flexibility, may be important.

The first series of models in which intramolecular electron transfer from a photo-excited porphyrin donor to a benzoquinone acceptor was unequivocally demonstrated was reported by Kong and Loach (3). They synthesised a series of compounds in which the tetra-aryl porphyrin donor and benzoquinone acceptor were linked by a poly-methylene chain of variable length (structures 1-3). The poly-methylene chain was attached to the donor and acceptor by ester groups. The authors interpreted quenching of the porphyrin fluorescence, relative to the unlinked porphyrin in a solution containing an equimolar amount of benzoquinone, as evidence for intramolecular electron transfer. Subsequent analysis of these compounds (4) resulted in the detection of light-induced EPR signals assigned to the porphyrin radical cation and the quinone radical anion.

A similar series of compounds (4-6), in which the ester groups were replaced by amide groups, showed similar behavior (5). In both of these series of compounds the interpretation of data was complicated by the flexible nature of the linkage connecting the porphyrin and the quinone. It was, however, possible to interpret the data obtained from these species in terms of two slowly equilibrating families of conformations

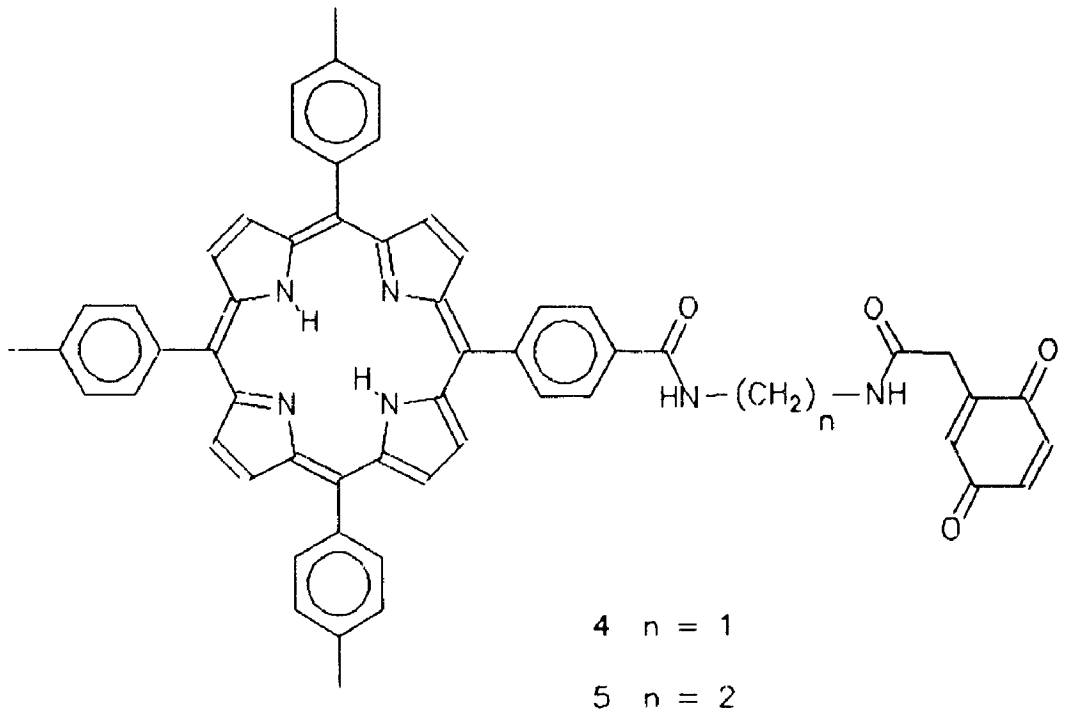
Figure 1-1: Compounds **1** - **6**



1 n = 1

2 n = 2

3 n = 3



4 n = 1

5 n = 2

6 n = 3

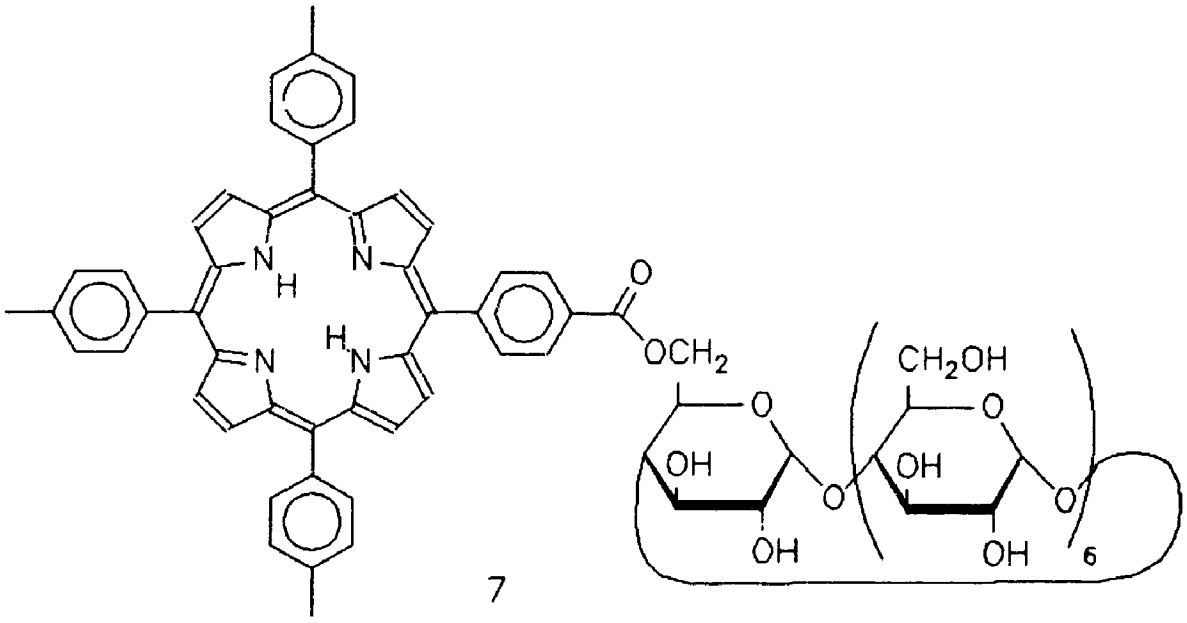
labelled "extended", in which the porphyrin and quinone were held apart, and "complexed", in which they were held together.

Although species such as those discussed above are capable of mimicking the initial step of photosynthesis (ie electron transfer from a photo-excited porphyrin donor to a nearby quinone acceptor) they suffer the severe disadvantage that the charge separated state quickly reverts to the ground state by reverse electron transfer. The challenge is, therefore, to design a system in which the forward rate of electron transfer is much faster than the rate of the reverse reaction.

Energetic Considerations:

The question of the dependence of the rate of electron transfer on the relative energies of the donor and acceptor and their radical cation and anion, respectively, has been the subject of several investigations. One of the first such investigations made use of the binding ability of β-cyclodextrin to provide rapid access to a variety of donor acceptor pairs (6). The tetra-aryl porphyrin donor was covalently linked to a β-cyclodextrin, (7), which was used to bind the potential electron acceptors. Photochemical excitation of the porphyrin resulted in electron transfer to the acceptor bound in the cyclodextrin. The EPR signal intensity from the porphyrin radical cation was found to rise rapidly as the reduction potential of the possible electron acceptor changed from -0.4 to -0.2 V (vs. NHE). The

Figure 1-2: Compound 7



7

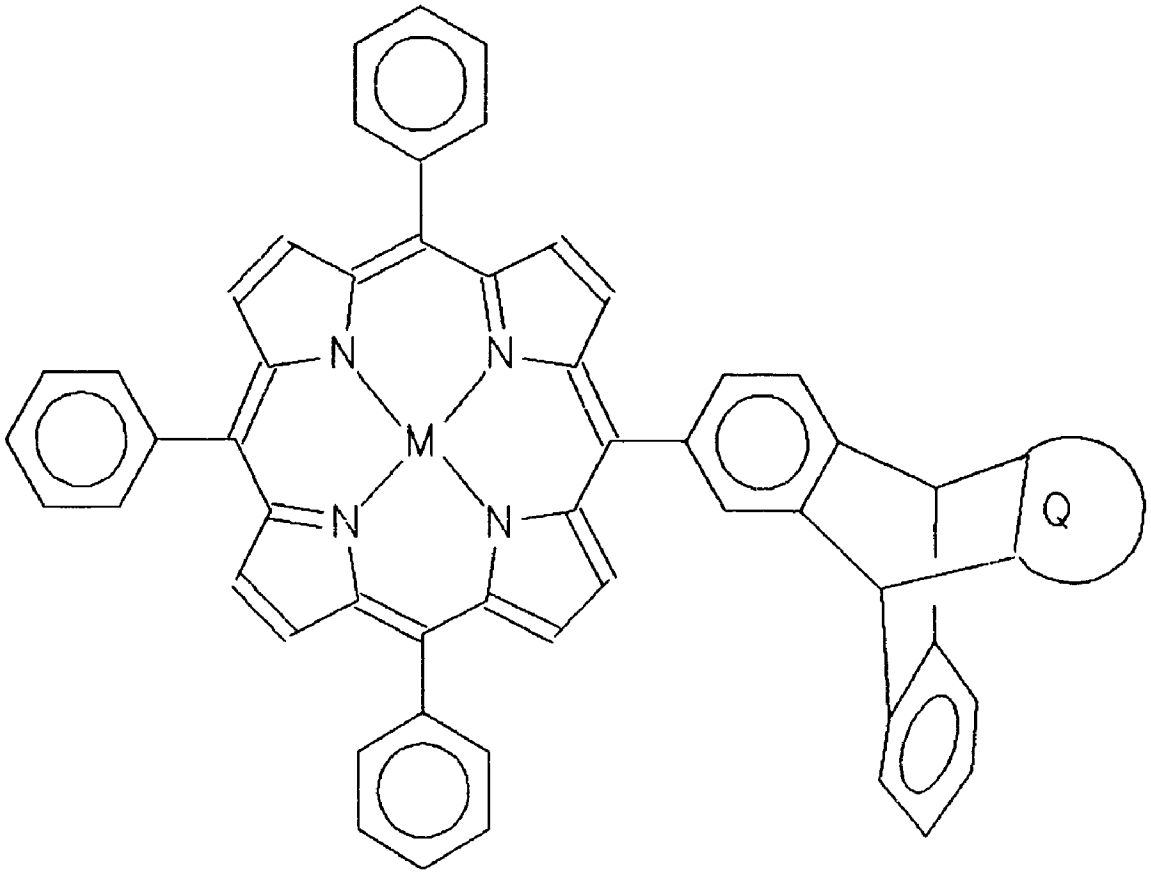
observation of non-linear Stern-Volmer kinetics for the porphyrin fluorescence quenching by the electron acceptors was taken as evidence that the electron acceptors were complexed within the cyclodextrin cavity.

Wasielewski *et al.* (7) have studied a tetra-aryl porphyrin, and its zinc complex, connected through a rigid triphenyltriptycene linkage to a series of three homologous quinones, (**8**-**13**). They report that the quantum yield of porphyrin fluorescence decreases as the electron transfer reaction becomes more energetically favourable. The rates of both the forward and reverse electron transfer reactions for these compounds were measured. The observed rates for the forward electron transfer increase as the reaction becomes more exothermic. The observed rates for the back reaction, which is more exothermic, decrease as the electron transfer exothermicity increases. This reversal of rate with increasing exothermicity is interpreted as an example of the inverted region predicted by Marcus theory.

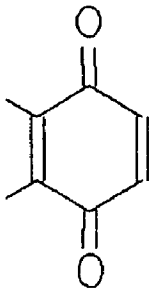
The observation of a slower rate constant for the reverse electron transfer has also been made by Schmidt *et al.* (8). This observation was made on a tetra-aryl porphyrin linked by a single amide linkage to benzoquinone (**14**).

Joran *et al.* (9) have studied a zinc octa-alkyl porphyrin linked through a [2,2,2]-bicyclooctane bridge to a series of 5-substituted and 5,6-disubstituted benzoquinones (**15**-**21**). The rate of electron transfer from the photo-excited porphyrin to the quinones was found to increase to a maximum value for

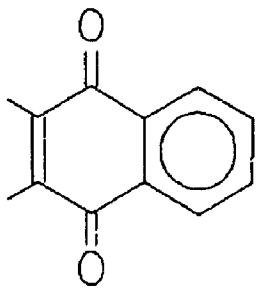
Figure 1-3: Compounds **8** - **13**



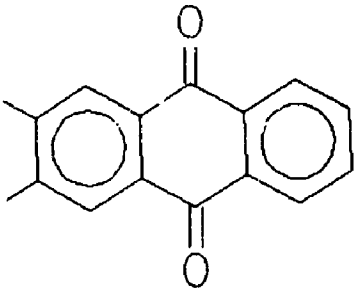
Q =



BQ



NQ



AQ

8 M = H_2 Q = BQ

9 M = H_2 Q = NQ

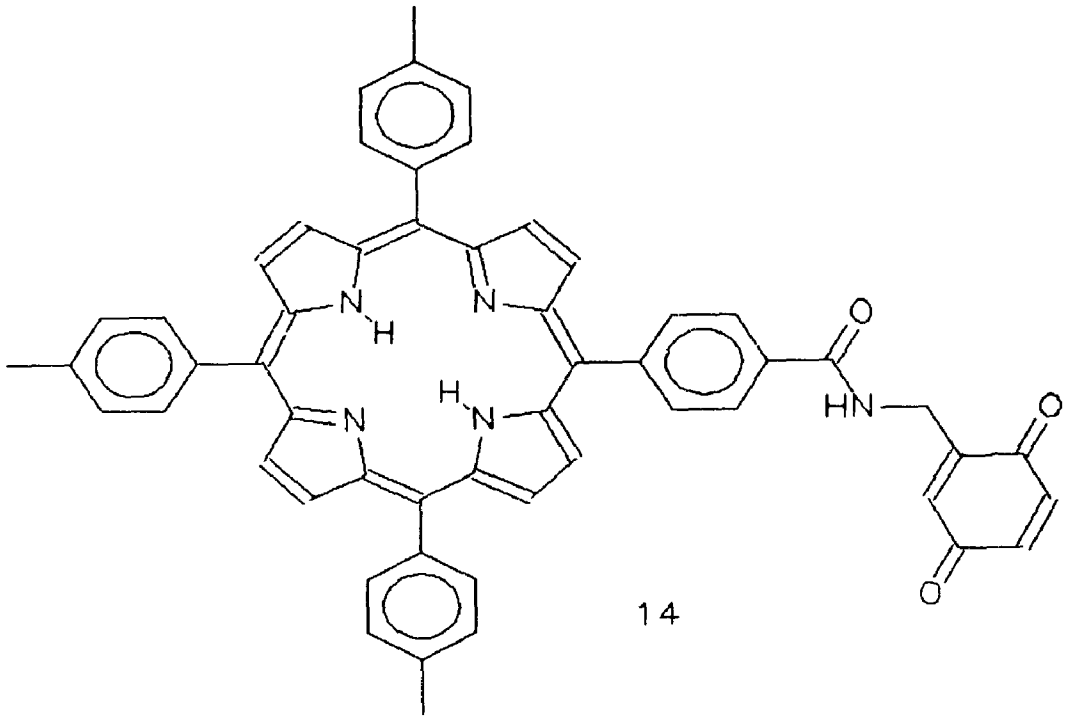
10 M = H_2 Q = AQ

11 M = Zn Q = BQ

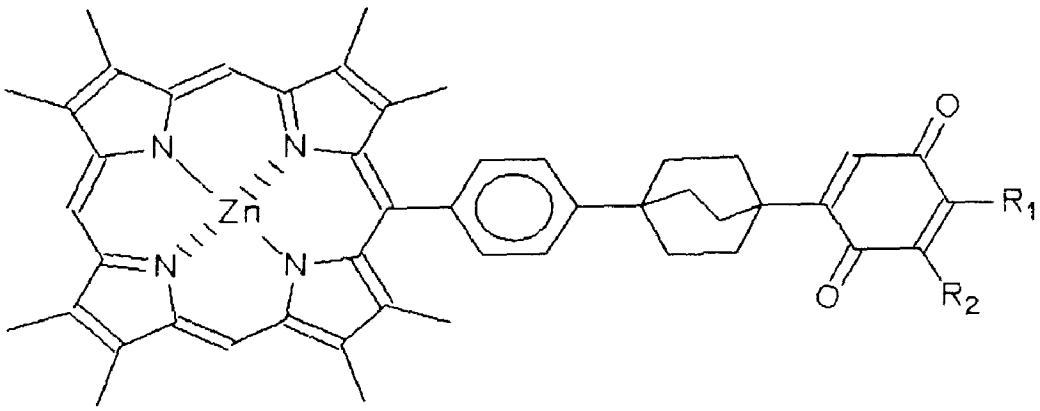
12 M = Zn Q = NQ

13 M = Zn Q = AQ

Figure 1-4: Compounds **14** - **21**



14



15 $R_1 = R_2 = CH_3$ 16 $R_1 = CH_3$ $R_2 = H$

17 $R_1 = R_2 = H$ 18 $R_1 = Br$ $R_2 = H$

19 $R_1 = Cl$ $R_2 = H$ 20 $R_1 = R_2 = Cl$

21 $R_1 = CN$ $R_2 = H$

the dichloro analog, and then to decrease for the more exothermic transfer to the 5-cyano analog. Similar behavior was observed in four different solvents. However, the rates of the reverse reactions were not measured.

In each of the series of experiments discussed above benzoquinone was found to be an excellent electron acceptor. The rate of electron transfer to benzoquinone was found to be similar to or faster than that to other potential acceptors. Benzoquinone was used as the electron acceptor in the models to be described in this study for this reason. A second major advantage to the use of benzoquinone is its already widespread use in other model systems; thus ready comparison with these systems is possible.

Solvent Considerations:

The question of solvent effects on the rate of intramolecular photo-induced electron transfer has been studied by Schmidt et al. (10). Using the species described above, (14), it was discovered that the rate of the forward electron transfer, k_{et}, varied over two orders of magnitude, and was apparently dependant on the solvent refractive index, n, and dielectric constant, ϵ. The relationship is given in equation 1-1.

$$-\ln(k_{et}) \propto (n^{-2} - \epsilon^{-1}) \qquad (1\text{-}1)$$

This relationship, which is predicted by Marcus theory, is based on the solvent contribution to the reorganization energy associated with electr transfer.

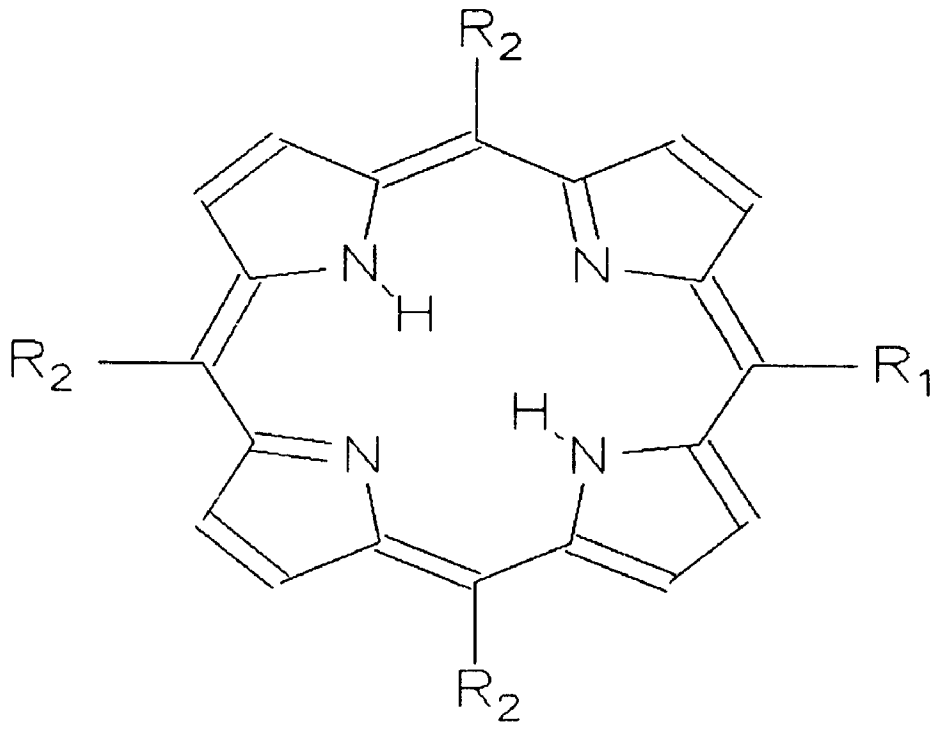
For binary solvent mi tures, excellent agreement was obtained between observed rates and those predicted by this treatment.

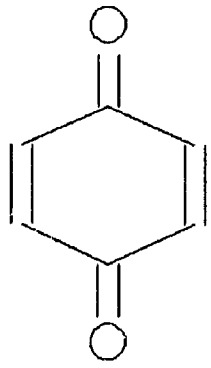
Donor Acceptor Sepa ion:

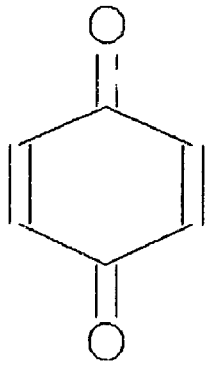
The relationship between the distance from the photo-excited donor to the acceptor and the rates of forward and reverse electron transfer is complex. In rigid systems where the donor, acceptor and linking unit monomer are kept constant, it is found that as the number of monomers in the linking unit increases, the rates for both forward and reverse electron transfer decrease. However, it is not possible to make comparisons from one family of model systems to another since changing the nature of the linkage, or the donor or acceptor, changes the rates of electron transfer, even if the distance between the donor and the acceptor has not changed. Moreover, in flexibly linked systems, as the number of linking unit monomers in the linkage increases the time averaged orientation and the maximum donor acceptor orbital overlap in the most favourable conformations change, in addition to the donor acceptor separation.

For the models in which the quinone acceptor is attached directly to one or more of the meso positions of the porphyrin ring (e.g. 22-23), the lifetime of the singlet excited

Figure 1-5: Compounds **22** - **24**



22 R_1 =  R_2 = Ph

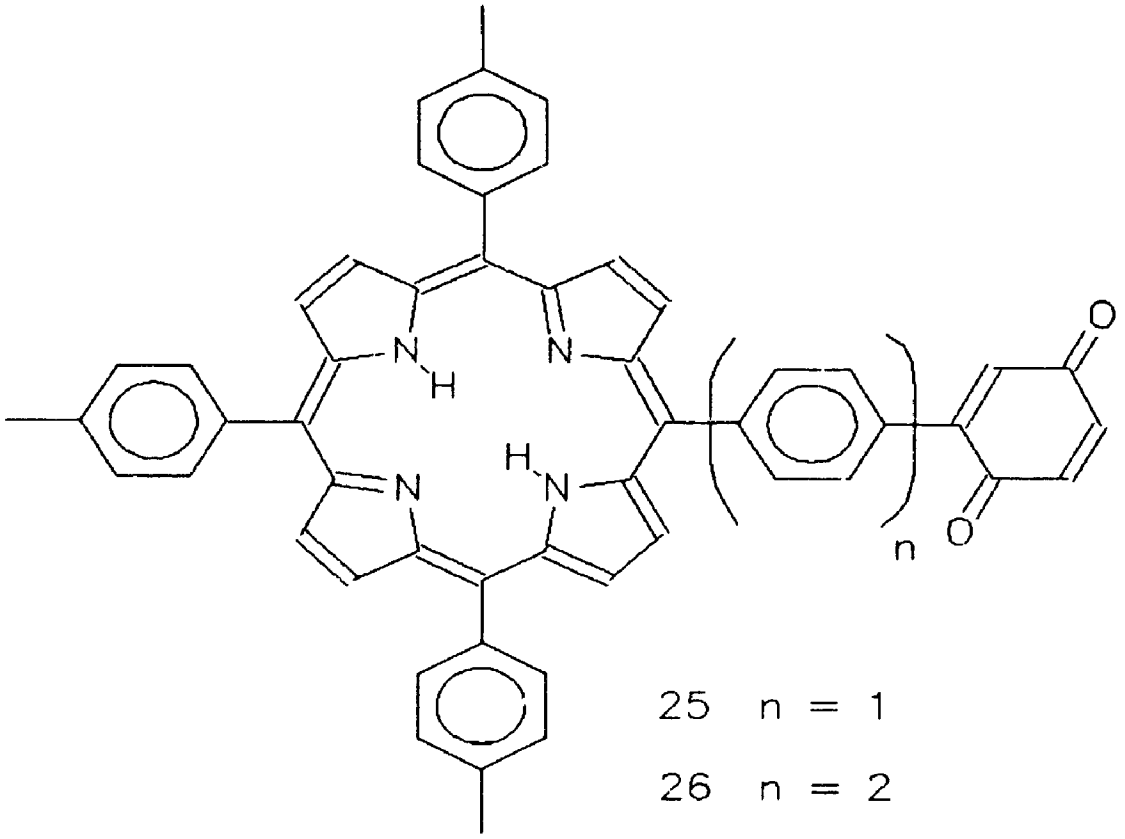
23 $R_1 = R_2 =$ 

24 $R_1 = R_2$ = Ph

porphyrin is less than 6 ps, compared to greater than 6 ns for the tetra-phenyl analog (24) (11). This corresponds to a forward electron transfer rate constant of greater than 10^{11} s^{-1} (12). Introducing a single phenyl ring between the porphyrin and quinone (i.e. 25) has little effect on the electron transfer rate constant; the minimum value has been determined to be 3.3×10^{10} s^{-1} (13). A second phenyl ring (i.e. 26) reduces the electron transfer rate constant to 2.7×10^{9} s^{-1} (13). All these values were determined in methylene chloride. Changing the solvent to benzene increases the effect of the second phenyl ring. In benzene the rate constants of electron transfer for 25 and 26 differ by a factor of ca. 100 (13).

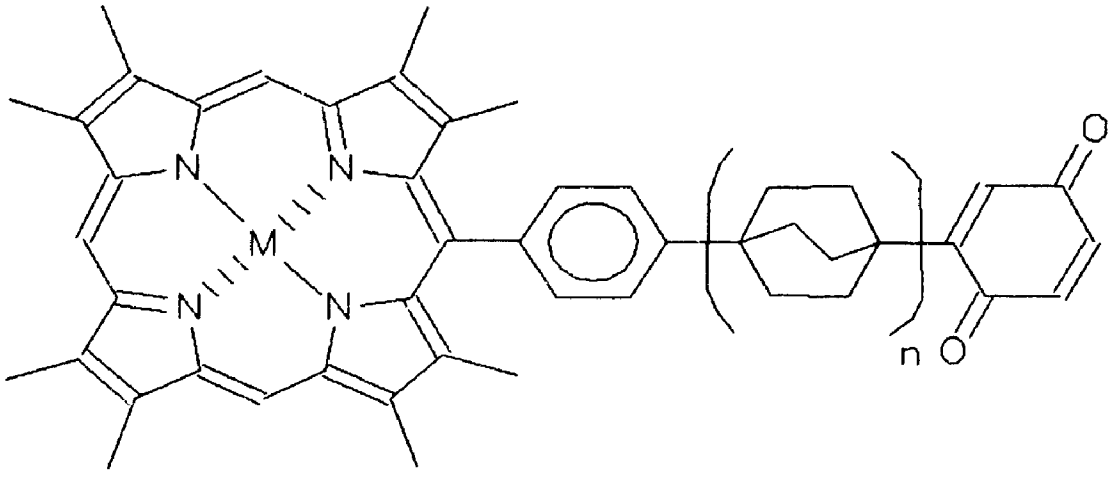
The model system with [2,2,2]-bicyclooctane as the linking unit monomer has also been studied (14). Using meso-phenyl octa-methyl porphyrin as the donor, the observed rate constants of electron transfer for n = 0,1,2 (i.e. 27-29) in benzene were 5.8×10^{9}, 1.5×10^{7} and $\leq 4 \times 10^{6}$ s^{-1}, respectively. The zinc porphyrin series (30-32) in benzene gave rate constants of 2.2×10^{11}, 1.5×10^{10} and $\leq 9 \times 10^{6}$ s^{-1}, respectively. This zinc porphyrin [2,2,2]-bicyclooctane linked system has been subjected to a theoretical analysis (15). This analysis concluded that electron transfer in this system proceeds by a superexchange, or hole transfer, mechanism. This mechanism uses the bonding orbitals (ie valence band) for transfer of the electron rather than the antibonding orbitals (ie conduction band). The drop

Figure 1-6: Compounds **25** - **32**



25 n = 1

26 n = 2



27 M = H_2 n = 0

28 M = H_2 n = 1

29 M = H_2 n = 2

30 M = Zn n = 0

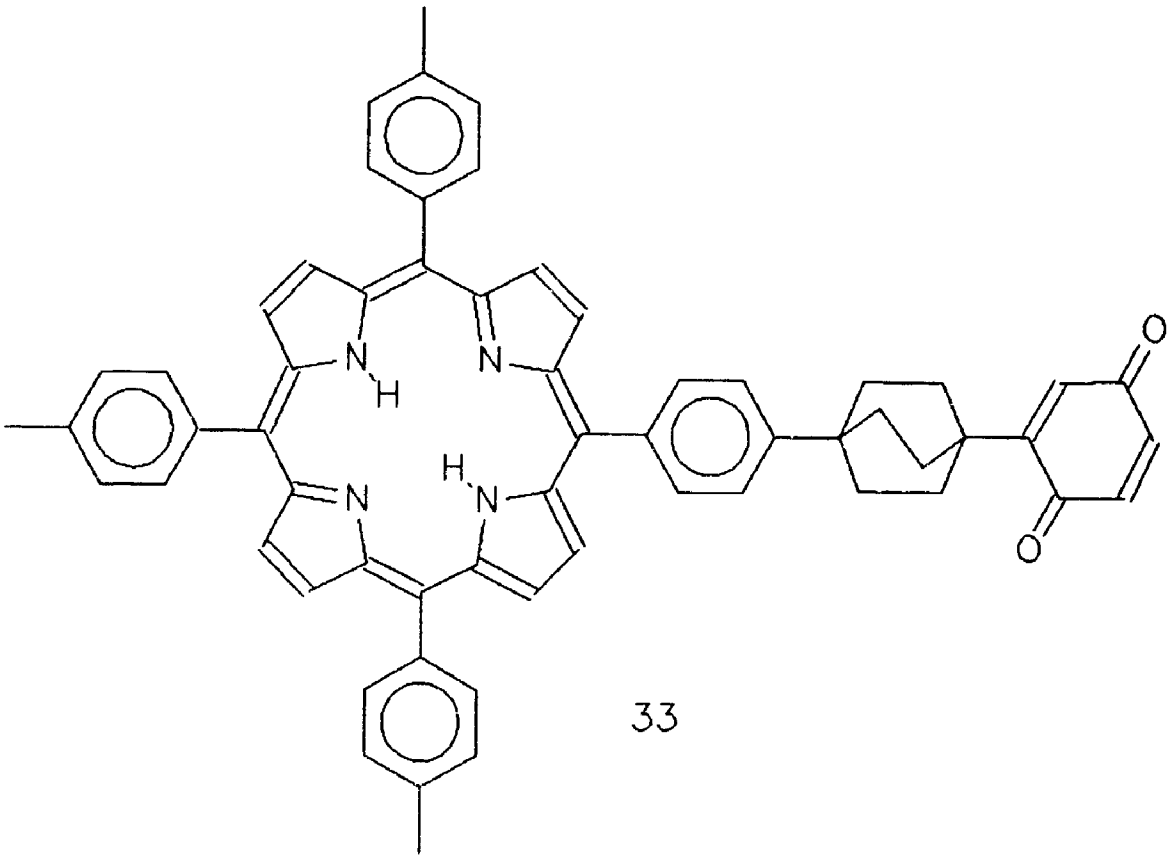
31 M = Zn n = 1

32 M = Zn n = 2

in the forward electron transfer rate constant is calculated to be a factor of 1500 per [2,2,2]-bicyclooctane unit, in reasonable agreement with the observed results (14). The drop in the reverse electron transfer rate constant is calculated to be only a factor of ca. 60. As a consequence of the superexchange mechanism, it is concluded that for porphyrins with higher energy excited states the drop in forward electron transfer rate constant with added [2,2,2]-bicyclooctane units will be even more severe. This is in agreement with the observations of electron transfer rate constants of 1×10^{10} for species 31 in 2-methyltetrahydrofuran (14b) and 1.6×10^{6} for the free base tetra-aryl analog (33) in the same solvent (16). The excited state energy of species 31 is lower than that of species 33 due to interaction of the metal atom orbitals with the porphyrin pi-system.

An indication of the confusing effect of lengthening a flexible linkage can be seen in species 4, 5 and 6 (5b). The fluorescence lifetimes of the short lived component (assigned to the conformers in which the methylene chain is folded such that the porphyrin and quinone are close in space) of these species in methylene chloride is 3.2, 1.8 and 3.1 ns respectively. The fluorescence lifetimes of the long lived components (assigned to the conformers in which the porphyrin and quinone are held apart) is 8.7, 6.3 and 9.2 ns.

Figure 1-7: Compound **33**



33

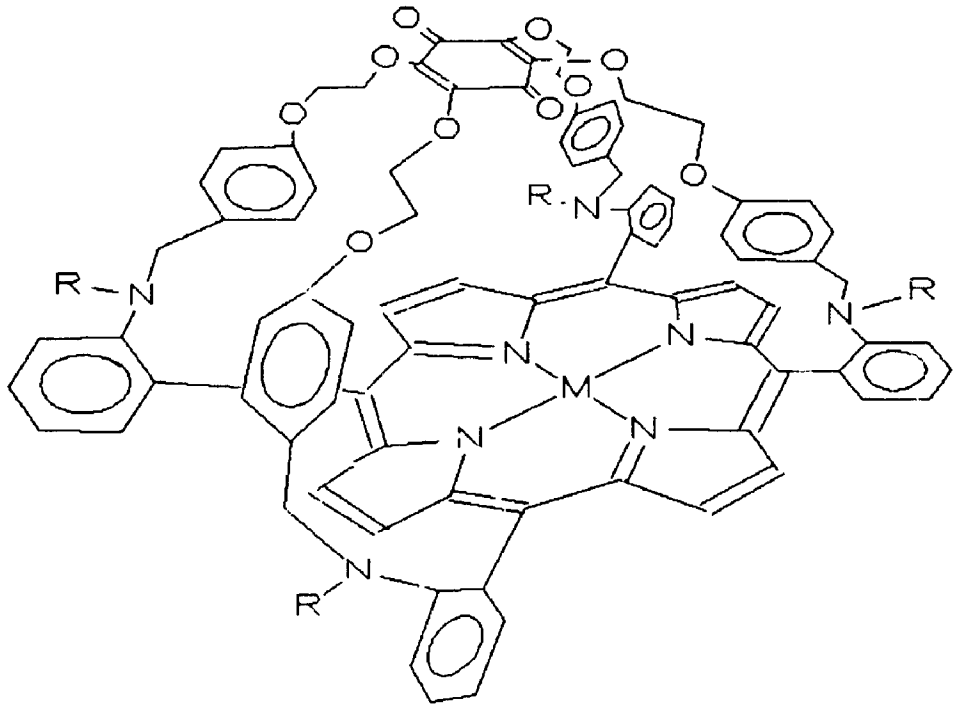
Donor Acceptor Orientation:

This is the most difficult parameter to control in model systems. Even with the rigidly linked species discussed above there is still the possibility for several rotamers, some or all of which may be important in electron transfer (15).

It is known that electron transfer can occur from a porphyrin to a quinone when they are allowed only edge to edge orientations, such as in species 22-33, or when they are allowed only face to face orientations, such as in the capped species 36-43.

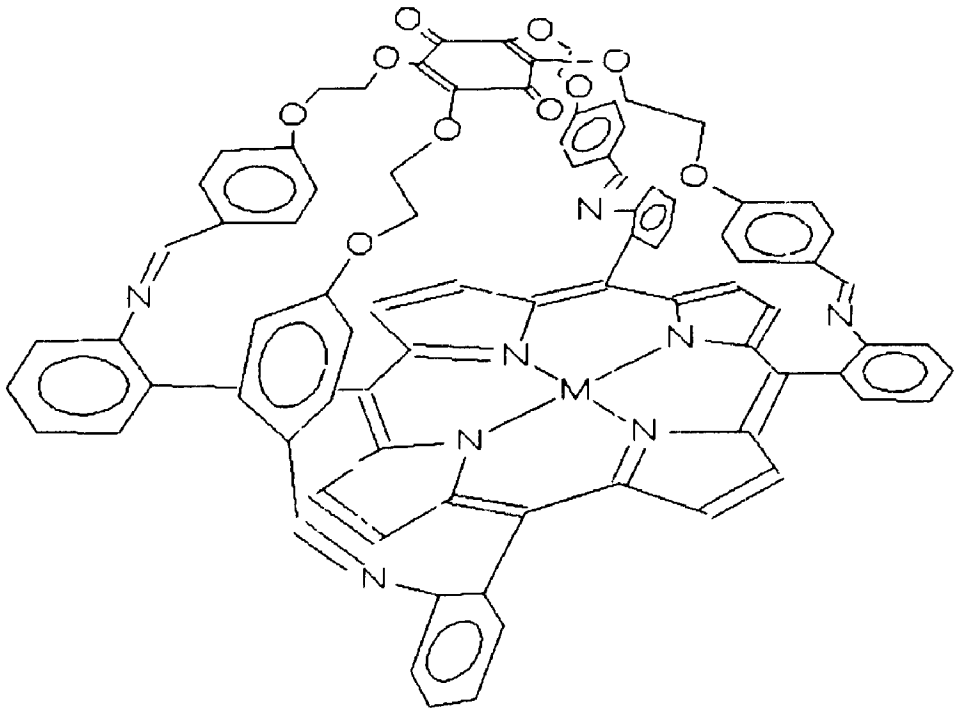
The most rigidly linked system, which allows for a face to face orientation between the porphyrin and the quinone, has been reported by Lindsey et al. (17). These species, (34-38), have the quinone held above the plane of the porphyrin by four covalent linkages. However, in these systems the quinone is not held completely rigid. There are two conformations present; introverted, in which the linkages are "folded" such that the porphyrin quinone separation is only 6.5 Å, and extroverted, in which the linkages are "extended" such that the porphyrin quinone separation is 8.5 Å. The non-metalated species 34 and 35 do not appear to be capable of intramolecular photoinduced electron transfer to the quinone. The fluorescence lifetime of the porphyrin excited state is not quenched relative to model compounds. The data, however, indicate that the free-base porphyrin excited state is being quenched by the benzylamine moieties (17c). The metalated species 36-38 behave in a similar fashion to each other,

Figure 1-8: Compounds **34** - **38**



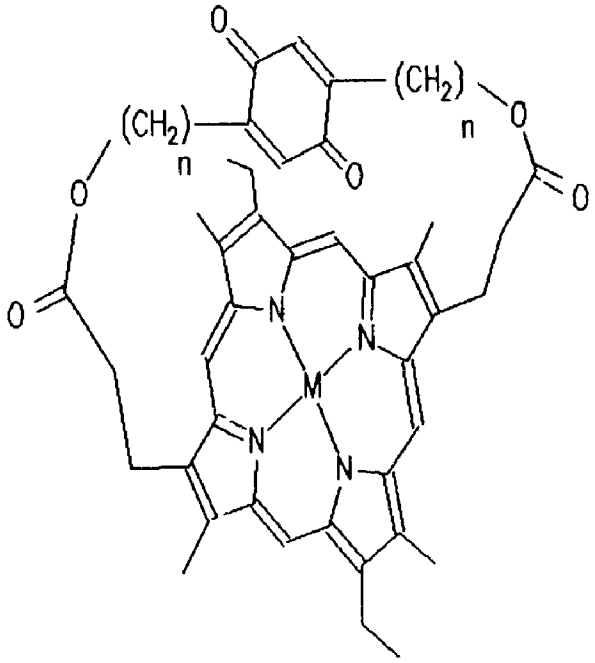
34 M = H_2 R = H 36 M = Zn R = H

35 M = H_2 R = Ac 37 M = Zn R = Ac



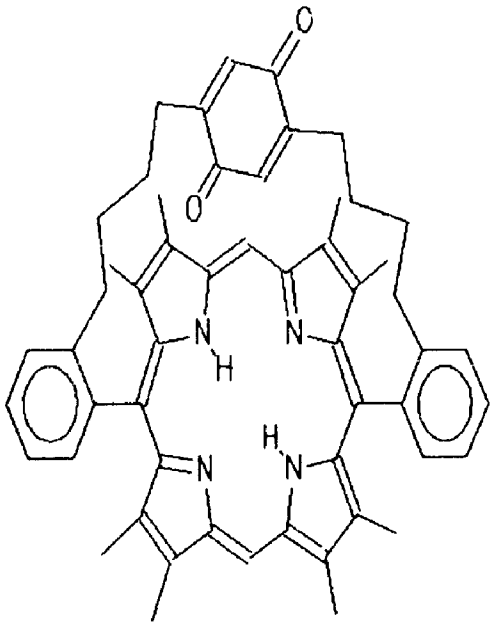
38 M = Zn

Figure 1-9: Compounds **39** - **44**

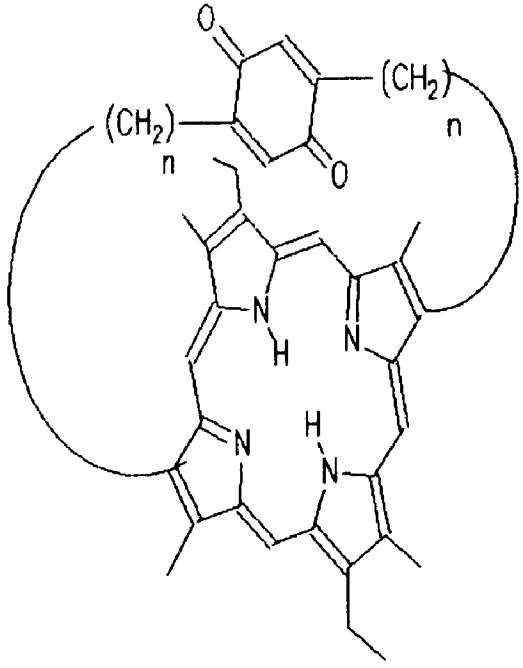


39 M = H_2 n = 2 41 M = Zn n = 2

40 M = H_2 n = 3 42 M = Zn n = 3



43



44 n = 5,6

indicating that the benzylamine moiety is not interfering. These species show two fluorescence lifetimes in the same ratio, corresponding to rate constants of intramolecular electron transfer of ca. 1.5×10^9 and 2.7×10^8 for the introverted and extroverted conformers, in acetonitrile at room temperature.

The less rigidly linked capped species 39-42 exhibit different behaviour. Both the free-base and zinc porphyrin fluorescence is quenched by the attached quinone, as detected by fluorescence quantum yield determinations in acetonitrile (18). If the zinc is replaced by magnesium, the porphyrin fluorescence is relatively unquenched. This difference is attributed to coordination of the magnesium by one of the quinone oxygens. This coordination would result in a perpendicular orientation of the quinone with respect to the porphyrin plane.

Species 40 and its magnesium analog were also studied by Irvine et al. (19). They found no difference between the fluorescence properties of these two compounds in methylene chloride. The forward and reverse rate constants of electron transfer for species 40 in a variety of solvents were also measured. The electron transfer rate constants for the reverse reactions are smaller than for the forward reactions, in agreement with the Marcus theory.

Quenching of free-base porphyrin fluorescence by benzoquinone held above the plane of the porphyrin has also been observed for species 43 in toluene (20). The related

species 44 has also been synthesised; however its fluorescence properties have not been investigated (21).

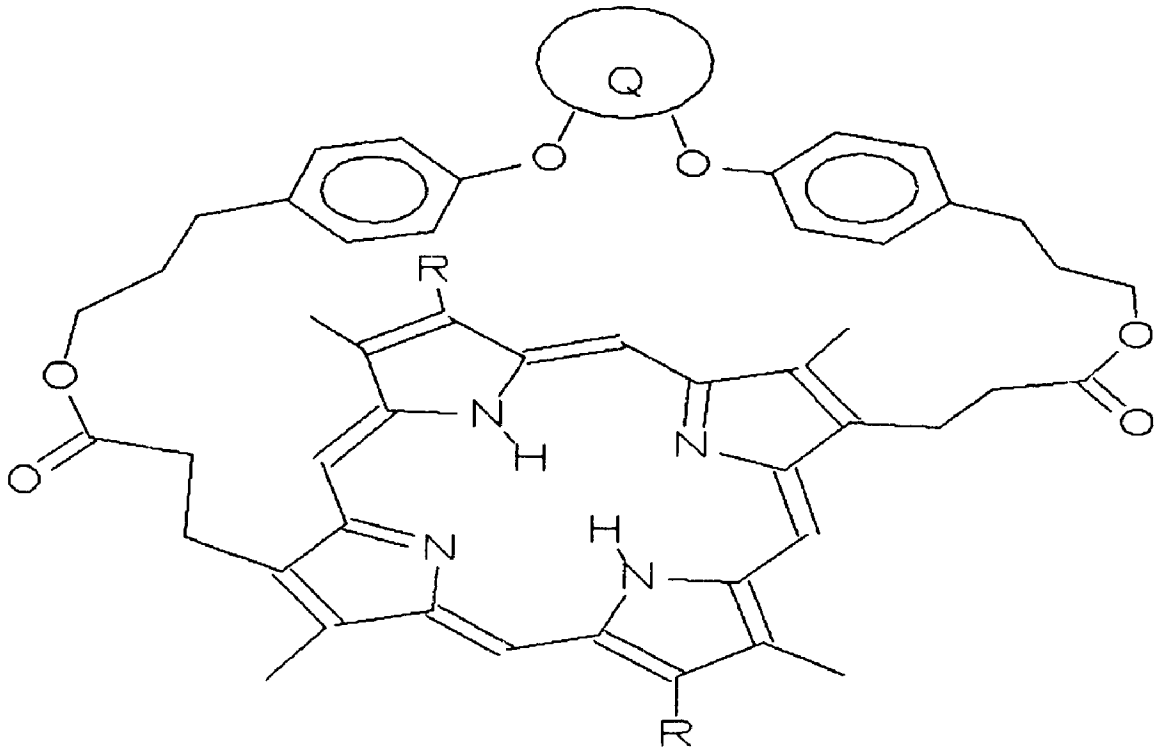
The interesting series of compounds 45, 46 and 47 have been synthesised by Osuka et al. (22). Free rotation within the linking units between the porphyrin and quinone, however, may mean that the desired orientation for each species is but one of a series of possible orientations. This would obscure any orientation effects, when the photophysical properties of these compounds are investigated.

A free-base tetra-aryl porphyrin with quinones held both above and below the plane of the porphyrin has been synthesised (23). The parallel conformation of the quinones relative to the porphyrin has been confirmed by X-ray analysis. This species, in which the porphyrin quinone distance is 3.42 Å, exhibits strong quenching of the porphyrin fluorescence in benzene solution.

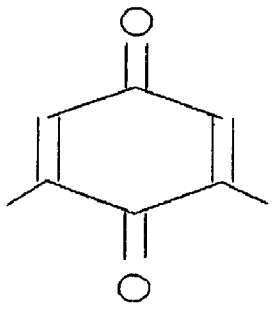
While the systems discussed above illustrate that photo-induced electron transfer is possible from both edge to edge and face to face orientations, they do not provide a measure of how the rate of electron transfer changes with the donor-acceptor orientation.

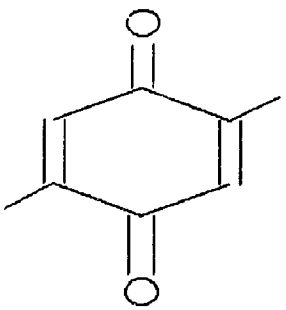
The more conformationally rigid species 48, in which a free-base mono-aryl octa-alkyl porphyrin is linked to a substituted naphthoquinone, has been synthesised (24). The forward electron transfer rate constant was measured to be 4.3×10^8 in methylene chloride. This compound is interesting in that the relative orientation of donor and acceptor can be

Figure 1-10: Compounds **45** - **47**



R = $C_{12}H_{25}$

45 Q = 

46 Q = 

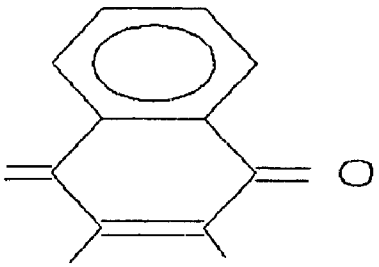
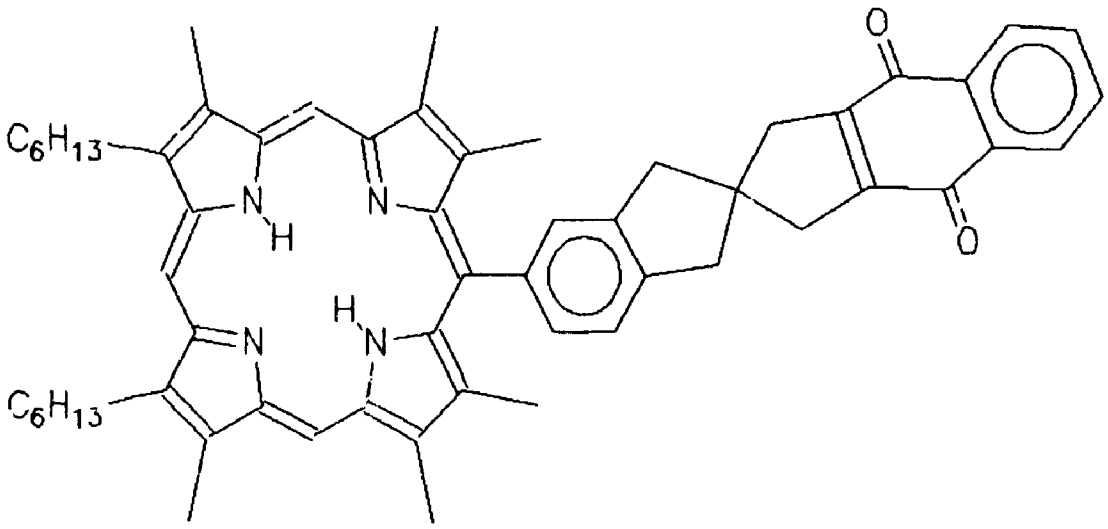
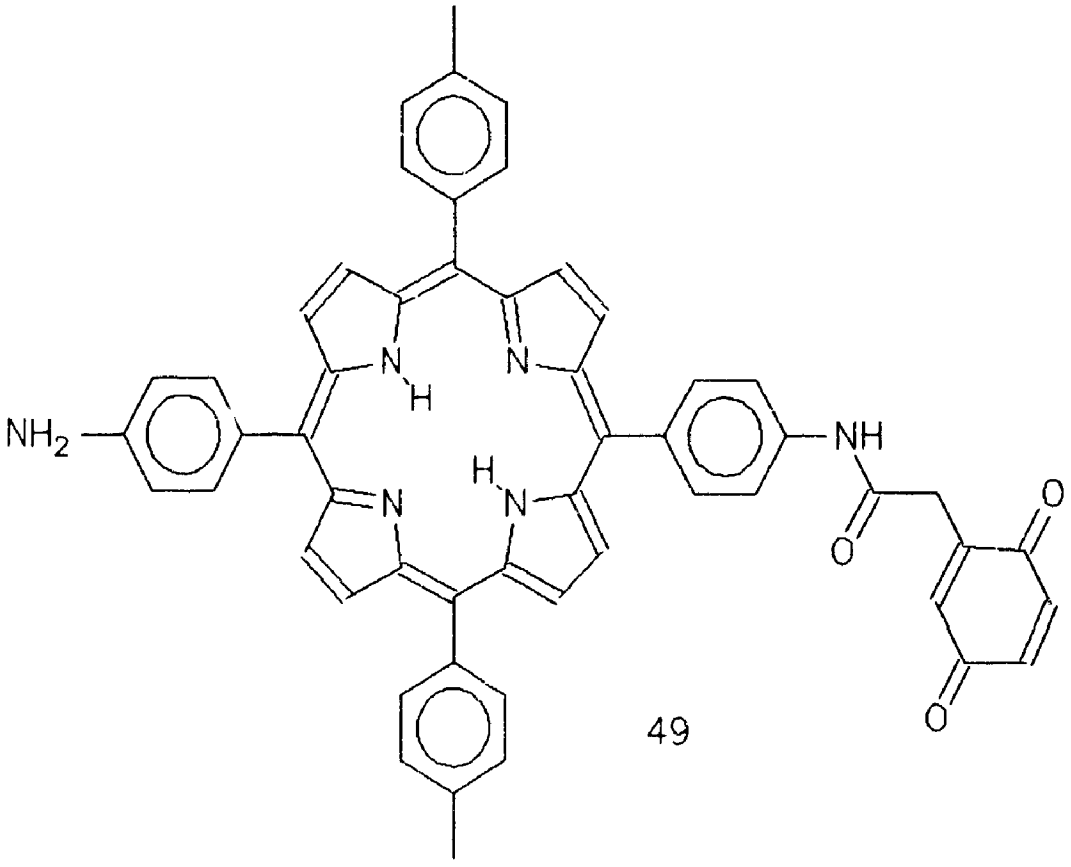
47 Q = 

Figure 1-11: Compounds **48** - **49**



48



49

determined with reasonable accuracy. There is, however, still the possibility of rotation about the phenyl porphyrin bond. Unfortunately, the lack of other systems, in which the relative donor acceptor orientation can be determined, prevents any conclusions regarding orientation from being drawn.

Linkage Structure:

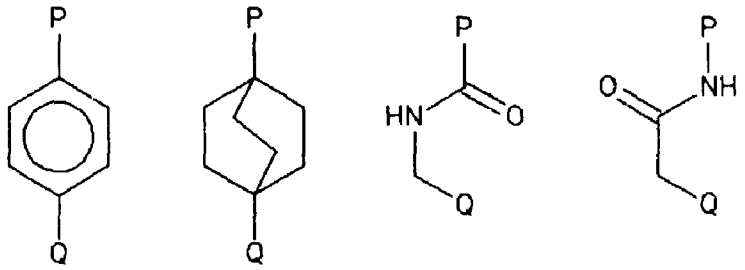
Compounds **14**, **26**, **33** and **49** have porphyrin quinone separations of 5.0 ± 0.5 Å. They each use benzoquinone as the electron acceptor, and they each have a free-base tetra-aryl porphyrin as the donor. Despite these similarities, in methylene chloride solution the forward electron transfer rate constants for these species vary by almost three orders of magnitude. This range, see Table 1-1, can only be attributed to changes in the nature of the linkage.

The effect of various types of hydrocarbon linkages on the rate of intramolecular photo-induced electron transfer has been analyzed from a theoretical standpoint (26). The results of the analysis indicate that a spirocyclobutane linkage should give the fastest electron transfer rate. This is a result of both the orientation of the orbitals and their energy levels.

Secondary Electron Transfer:

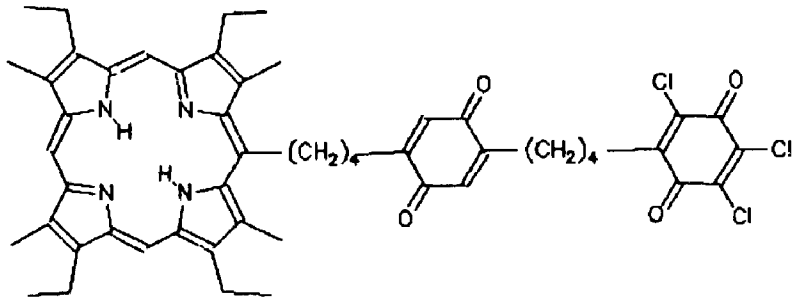
A strategy for stabilizing the charge separated state following photoinduced electron transfer is to introduce

Table 1-1: k_{et} values for various linked porphyrin-quinone species

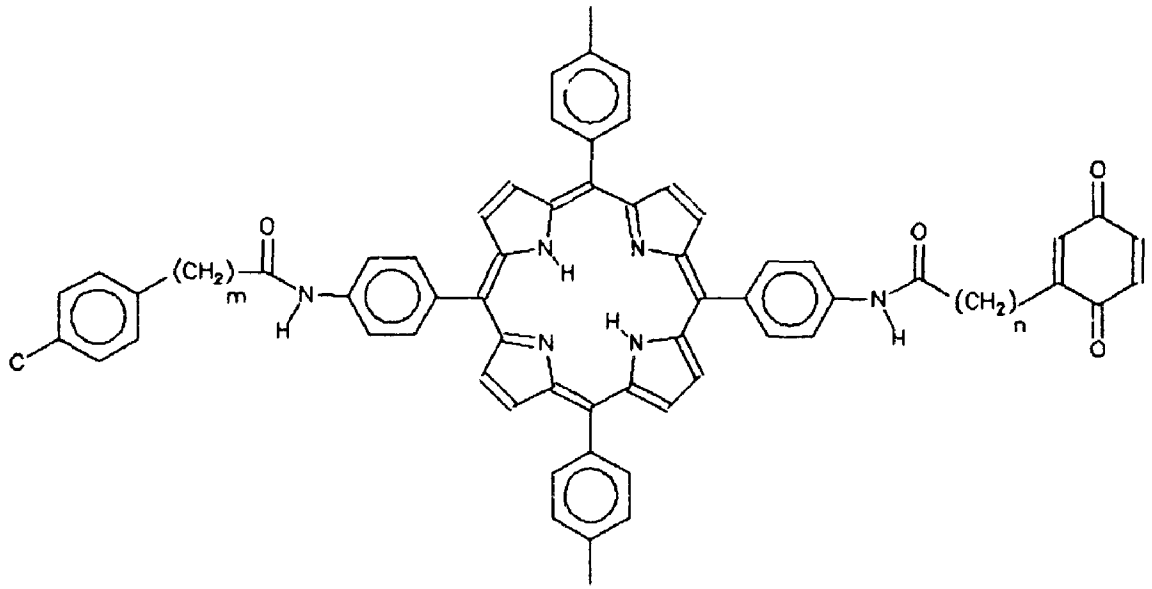


compound number	26	33	14	49
k_{et} (CH_2Cl_2)	2.7×10^9	1.5×10^7	8.1×10^8	9.9×10^9
reference number	13	16	10a	25

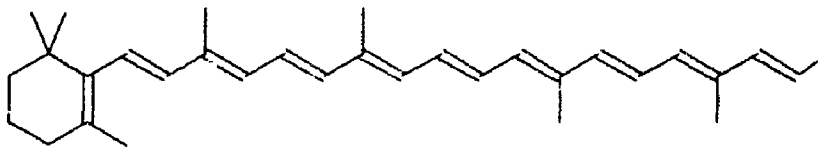
Figure 1-12: Compounds **50** - **56**



50

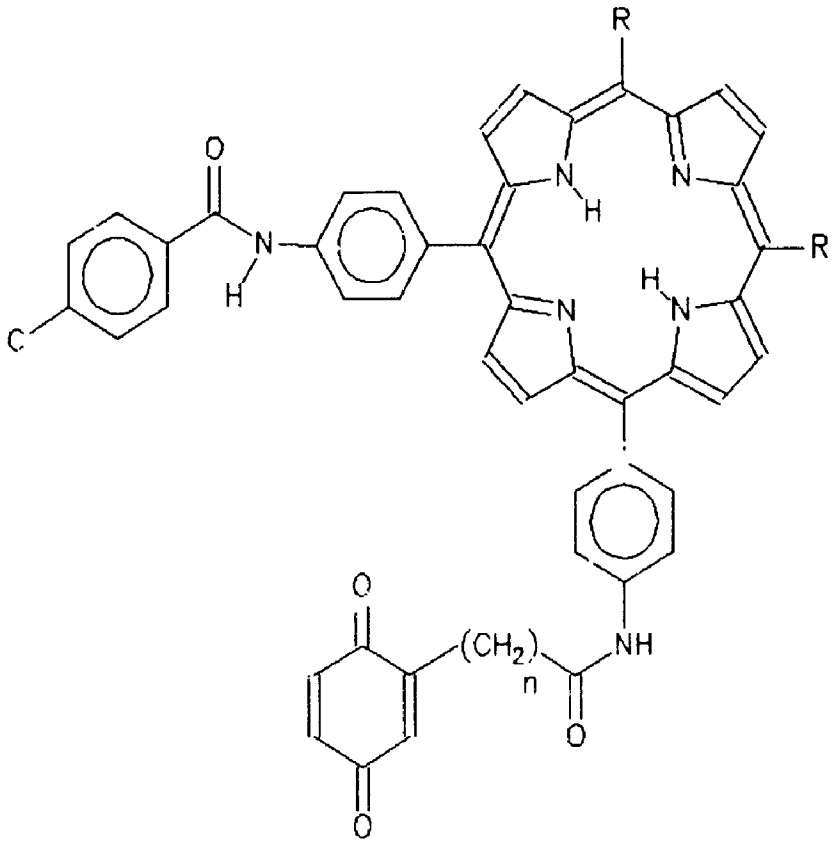


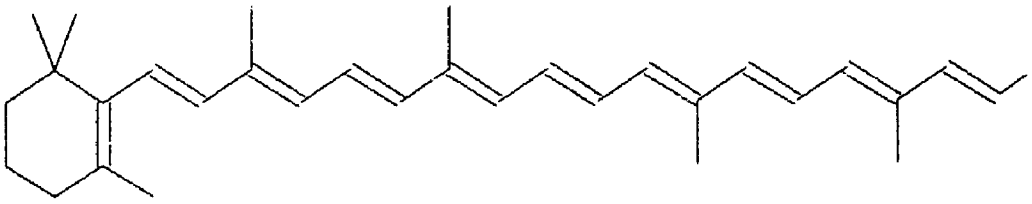
C =



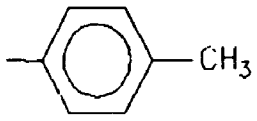
51 n = 0 m = 0		52 n = 1 m = 0	
53 n = 2 m = 0		54 n = 3 m = 0	
55 n = 4 m = 0		56 n = 1 m = 1	

Figure 1-13: Compounds **57** - **58**





= C

57 n = 2 R = 

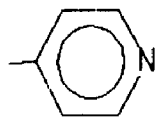
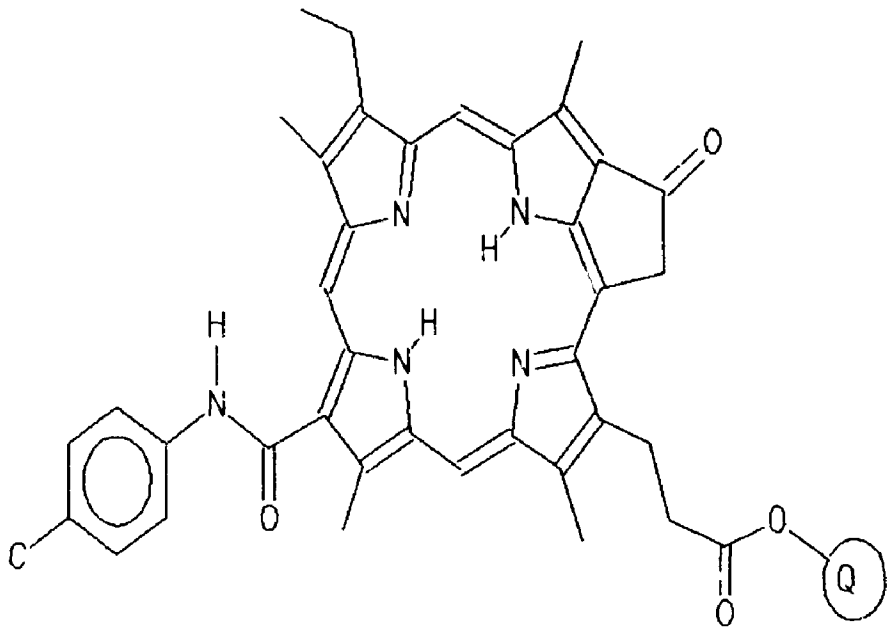
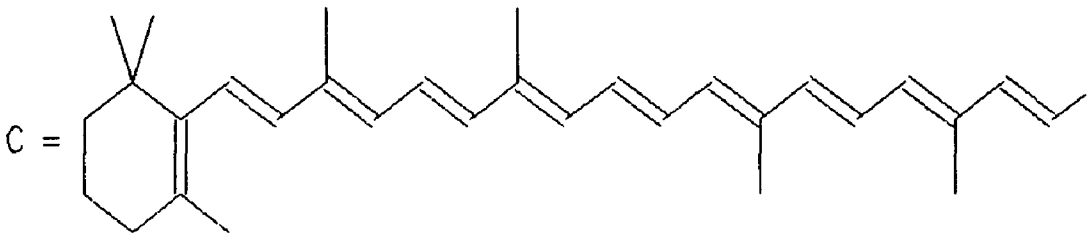
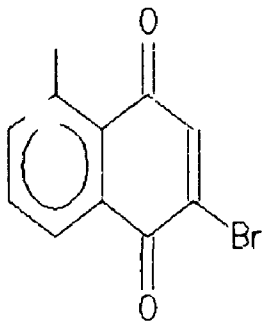
58 n = 1 R = 

Figure 1-14: Compounds **59** - **60**





59 Q = 

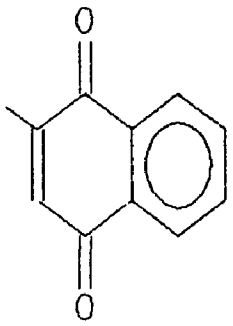
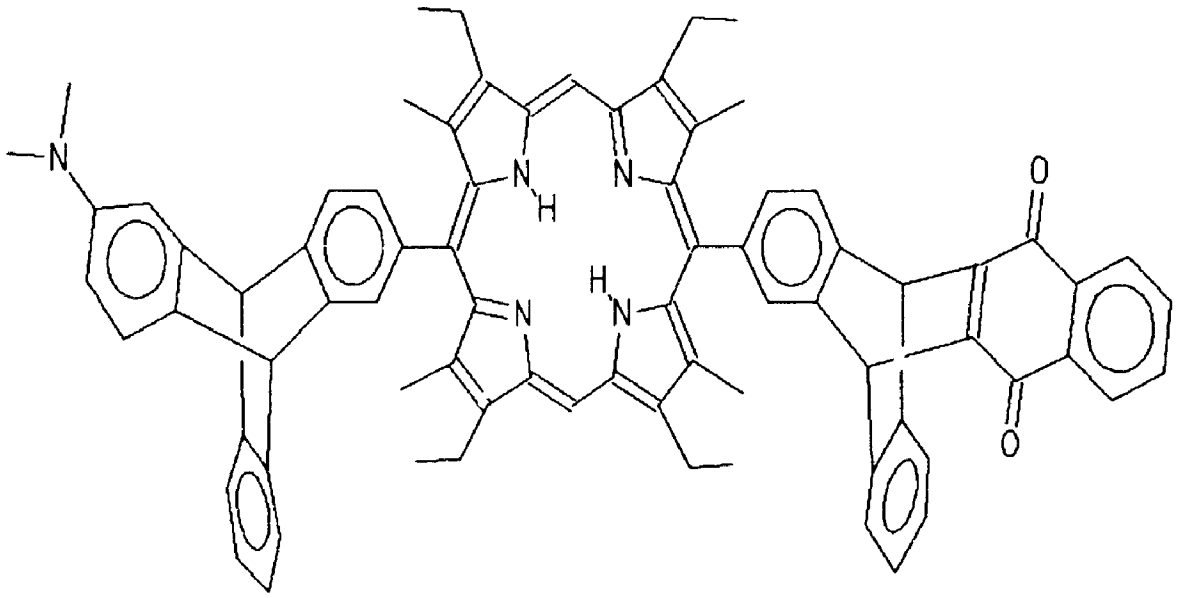
60 Q = 

Figure 1-15: Compound **61**

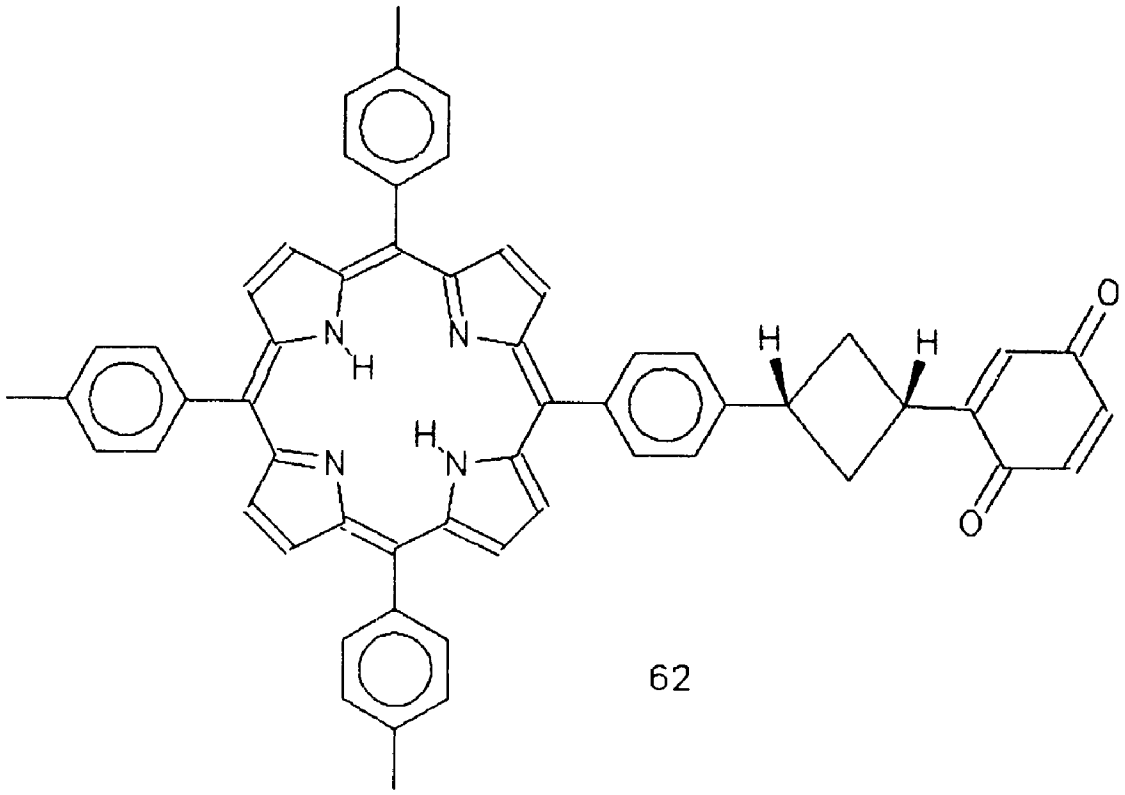


51

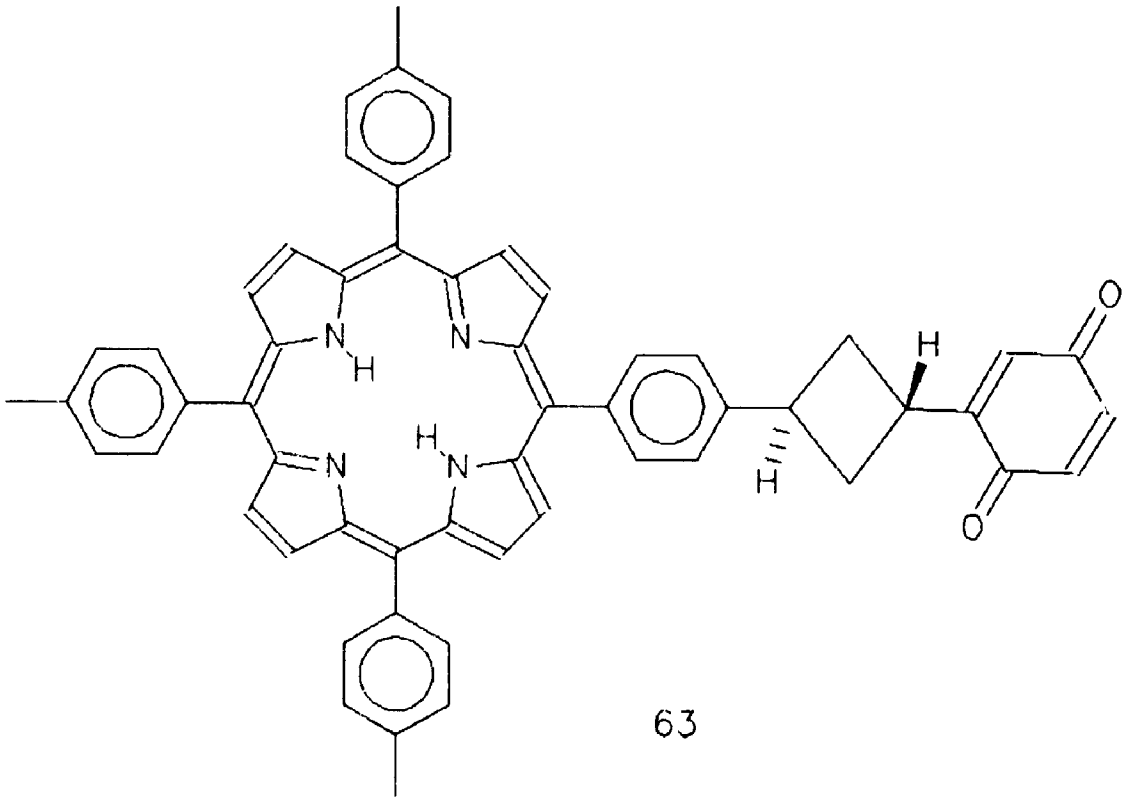
either a secondary acceptor, such as in species 50 (27), or a secondary donor, such as in species 51-61 (28-31). The role of the secondary acceptor or donor is to allow a ground state electron transfer to occur following the primary photoinduced electron transfer. This ground state electron transfer can occur from the reduced primary acceptor to the secondary acceptor or from the secondary donor to the oxidized primary donor. This subsequent electron transfer allows for enhanced separation of charge following the initial electron transfer, and thereby enhanced stability of the charge separated state. This approach has lead to a lengthening of the lifetime of the charge separated state from ca. 1.5×10^{-7} seconds to more than 1×10^{-6} seconds (28). It should be noted that the natural reaction centers of green plants employ a strategy of successive electron transfers to minimize the back reaction.

The objective of the study described in this thesis was to synthesise and analyze the cyclobutane linked tetra-aryl porphyrin benzoquinone species 62 and 63. These species provide an excellent example of a system in which the nature and number of bonds between the donor and acceptor is constant, yet the edge to edge separation is different. Thus, these species provide a test of the through-bond versus through-space nature of the electron transfer. At the time this study was commenced, there was uncertainty regarding the mechanism by which the electron was transferred from the donor to the acceptor. Since that time, evidence in favour of a

Figure 1-16: Compounds **62** - **63**



62



63

through bond mechanism has been compiled and this mechanism is now generally accepted. Further, at the time this study was commenced, this system represented the shortest rigid hydrocarbon linkage and as such was of interest for comparison with other rigid systems. Since that time species **48** has been described. However, **48** is not a tetraphenyl porphyrin and cannot be compared with systems such as **14**, **26**, **33**, and **49**.

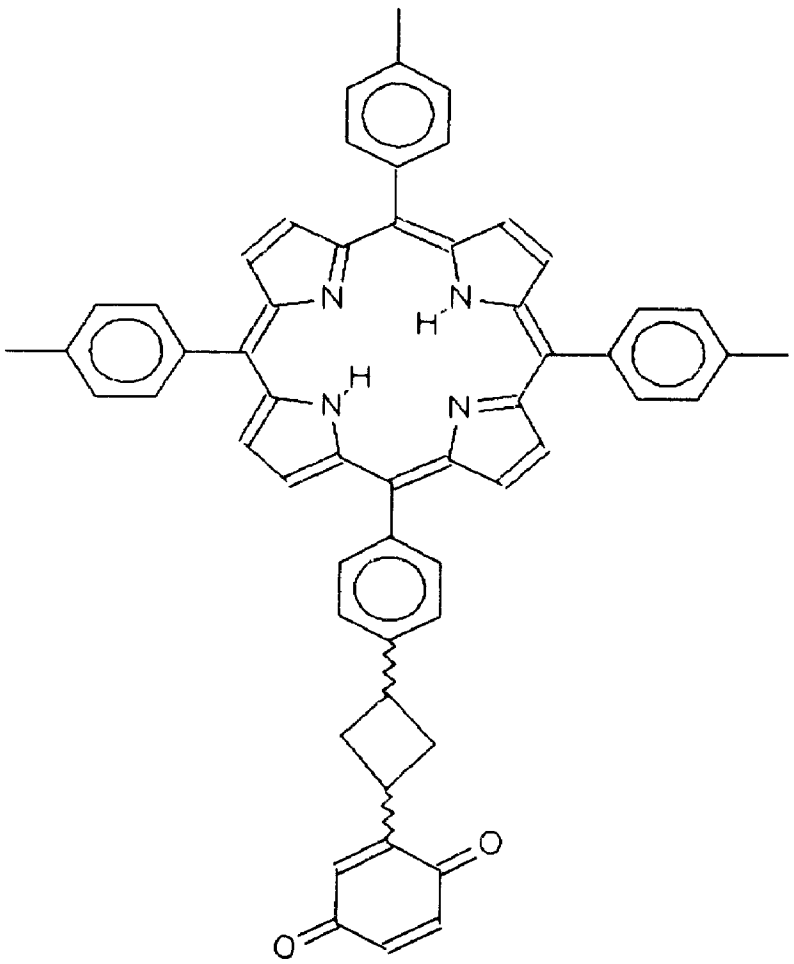
(B) RESULTS and DISCUSSION

i - Synthesis

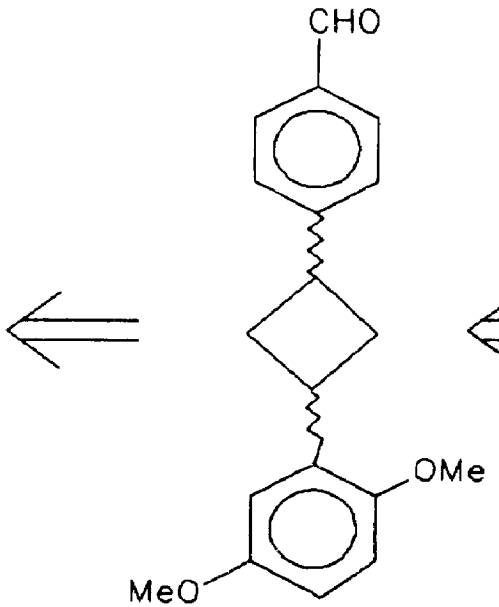
The original approach to the synthesis of the cyclobutane linked porphyrin-benzoquinone species 62 and 63 was to react an appropriately substituted 1,3-ditosylate with an appropriately substituted activated methylene compound in the presence of 2 equivalents of base, as outlined in Scheme 1-1. This approach is similar to that used for the synthesis of a range of compounds containing the cyclobutane moiety (32). The species initially chosen for this cyclobutane ring forming reaction were 2-(2,5-dimethoxyphenyl)-1,3-propanediol ditosylate 66 and 2-(4-(carboethoxymethyl)phenyl)-1,3-dioxolane 67. Once the cyclobutane ring was formed, the aldehyde could be regenerated by removal of the dioxolane protecting group. Combining the free aldehyde with pyrrole and p-tolualdehyde in refluxing propionic acid would yield the dimethoxyphenyl porphyrin, analogous to the procedure described by Anton and Loach (33). The dimethoxyphenyl ring could then be converted into the benzoquinone by sequential treatment with BBr_3 and PbO_2 (5). A similar approach, starting from ethyl 2,5-dimethoxy-phenyl-acetate 68, 2-(4-(carboethoxymethyl)phenyl)-1,3-dioxolane 67 and pentaerythritol tetratosylate 69 would yield the next higher homologue 70, as outlined in Scheme 1-2.

The initial synthetic targets were the ditosylate 66 and the phenylacetate 67. The planned approach to the ditosylate

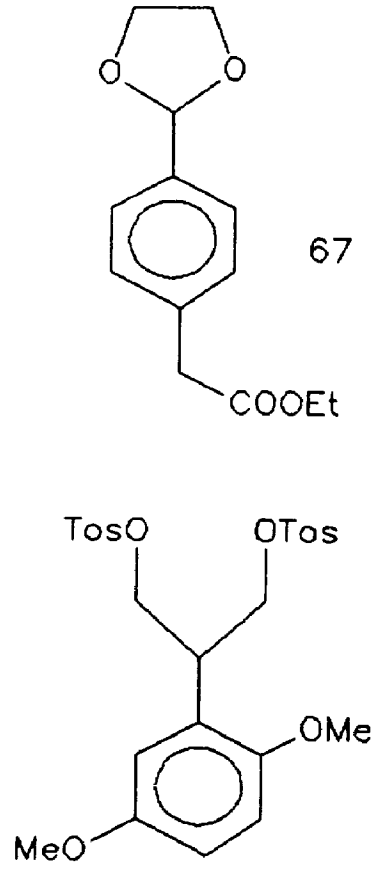
Scheme 1-1: Initial planned synthetic approach to compounds **62** and **63**



62 63

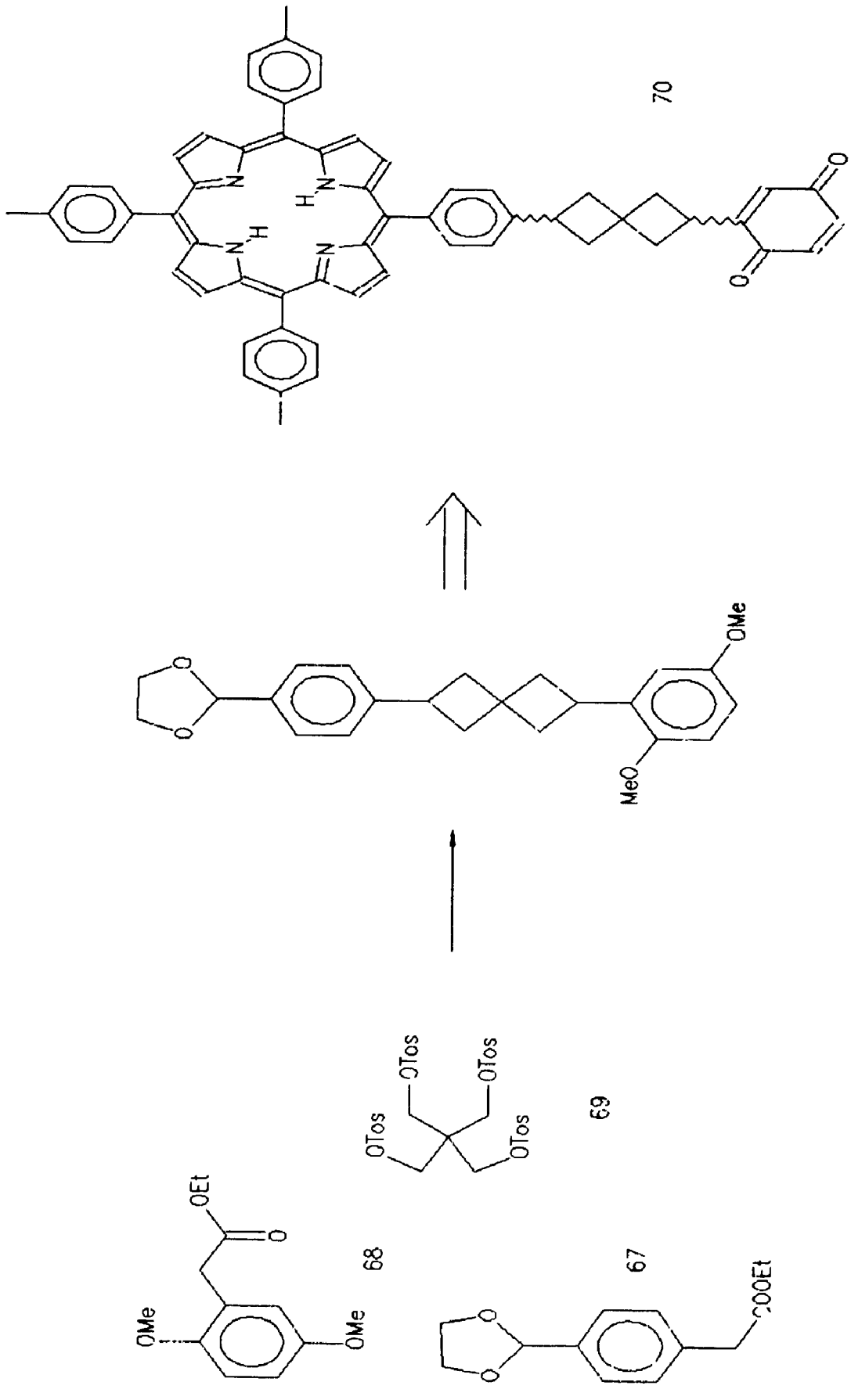


64 65



66

Scheme 1-2: Planned approach to compound **70**

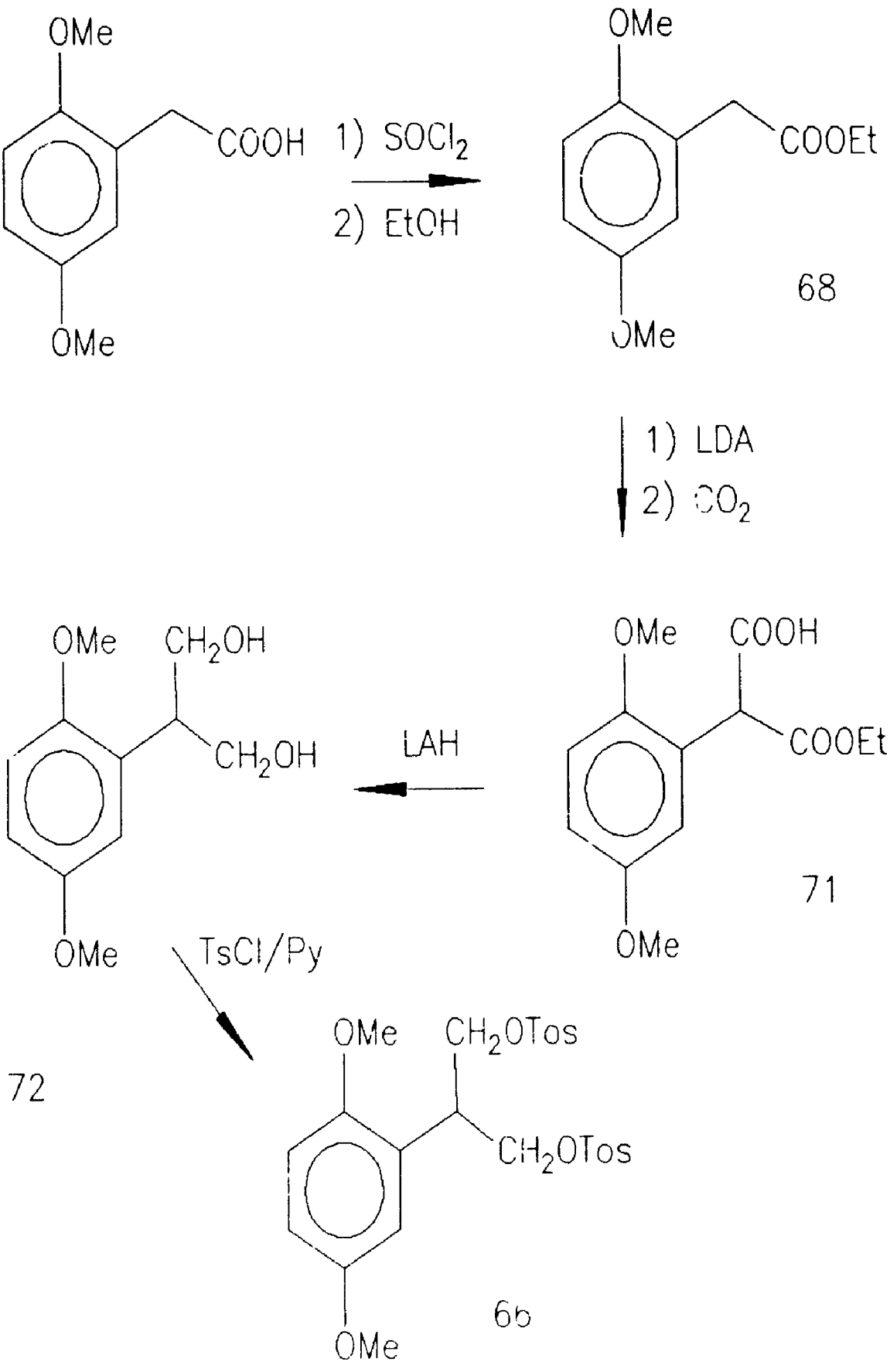

70
OMe
MeO
OTos
OTos
OTos
OTos
69
OEt
O
OMe
OMe
68
67
OOEt

utilized 2,5-dimethoxyphenyl-acetic acid as the starting material and is outlined in Scheme 1-3.

The 2,5-dimethoxyphenyl-acetic acid was first esterified, via the acid chloride, with ethanol. It was deemed necessary to proceed via the acid chloride due to the acid sensitive nature of the dimethoxyphenyl ring (the methyl ethers are easily cleaved by acid). Ester formation was confirmed by infra-red spectroscopy, which revealed a band at 1740 cm^{-1} in the product. The ^1H NMR spectrum of the ester indicated that the dimethoxy-phenyl ring had survived the thionyl chloride treatment. The mass spectrum of the product (parent ion at m/e = 224 and major fragment at m/e = 151 corresponding to α cleavage of the carboethoxy group) is consistent with the expected pattern for 68.

The ethyl 2,5-dimethoxyphenyl-acetate 68 was then carboxylated at the alpha position by treatment with lithium diisopropylamide to generate the anion, followed by bubbling of carbon dioxide through the reaction medium. The resulting carboxylate was protonated during work-up. The occurrence in the infra-red spectrum of carbonyl bands at 1730 and 1720 cm^{-1} as well as the combination band at 1775 cm^{-1} is consistent with the formation of the desired ethyl 2-(2,5-dimethoxy-phenyl)malonate 71. The ^1H NMR spectrum of the product showed the absence of the singlet at 3.59 ppm assigned to the benzylic methylene in 68 and the appearance of a singlet at 4.92 ppm, which integrated to 1 proton, attributed to the benzylic methine of 71. The mass spectrum of the product

Scheme 1-3: Synthetic route to compound **66**


OMe
COOH
OMe
1) SOCl2
2) EtOH
OMe
COOEt
OMe
68
1) LDA
2) CO2
OMe
CH2OH
CH2OH
OMe
LAH
OMe
COOH
COOEt
OMe
71
TsCl/Py
72
OMe
CH2OTos
CH2OTos
OMe
6b

(parent ion at m/e = 268 and major fragment at m/e = 224 corresponding to decarboxylation) is consistent with the expected pattern for 71.

The ethyl 2-(2,5-dimethoxyphenyl)malonate 71 was reduced with lithium aluminum hydride to give 2-(2,5-dimethoxyphenyl)-1,3-propanediol 72. The absence of a carbonyl band in the infra-red spectrum and the presence of a large band at 3300 cm^{-1} is consistent with the formation of the diol. The ^1H NMR spectrum showed a multiplet at 3.49 ppm which integrated to 1 proton, a doublet of doublets at 3.90 ppm, J = 5 and 12 Hz, which integrated to 2 protons, and a doublet of doublets at 3.99 ppm, J = 7 and 12 Hz, which integrated to 2 protons. These signals were assigned respectively to the benzylic methine and the two sets of diastereotopic protons on the methylene carbons neighbouring it. The mass spectrum of the product, parent ion at m/e = 212, is consistent with the diol 72.

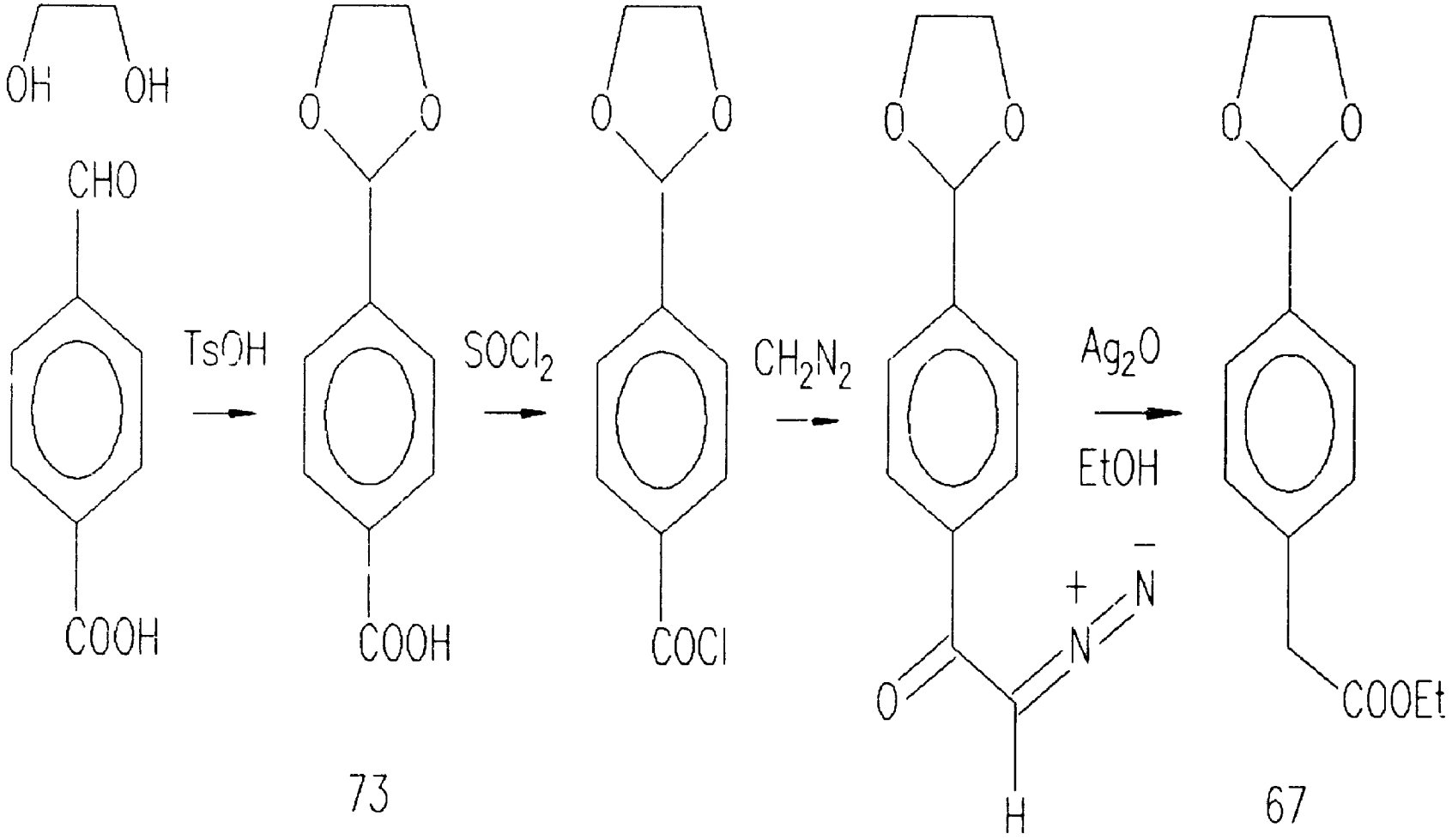
Treatment of 2-(2,5-dimethoxyphenyl)-1,3-propanediol 72 with p-toluenesulfonyl chloride in pyridine resulted in the formation of 2-(2,5-dimethoxyphenyl)-1,3-propanediol ditosylate 66. The infra-red spectrum of the product revealed the absence of the O-H stretch at 3300 cm^{-1}. The ^1H NMR spectrum of the product showed a singlet at 2.44 ppm, a doublet at 7.29 ppm, J = 8 Hz, and a doublet at 7.66 ppm, J = 8 Hz. These signals integrated to 6, 4 and 4 protons respectively. This indicated that two tosylate groups had been incorporated into the product, as desired. The mass

spectrum of the product (parent ion at m/e = 520 and major fragment at m/e = 348 corresponding to the loss of toluene sulfonic acid) is consistent with the expected pattern for 66.

The planned approach to the phenylacetate 67 utilized p-carboxybenzaldehyde as the starting material and is outlined in Scheme 1-4.

The aldehyde functionality was first protected as the ethylene acetal. This was effected using the method of Denny et al (34). The p-carboxybenzaldehyde was refluxed with ethylene glycol and a catalytic amount of p-toluene sulfonic acid in dry benzene using a Dean-Stark water entrainment head. Work-up of the reaction involved evaporation of the benzene, followed by dissolving the crude product in aqueous sodium hydroxide with the aid of heat. The product was precipitated from the cooled solution by the addition of glacial acetic acid. The product was isolated by dissolving it in chloroform, washing with water then drying and evaporating the chloroform. This involved work-up was necessary to hydrolyse any esters which may have been formed between the carboxylic acid functionality of the desired 2-(4-carboxyphenyl)-1,3-dioxolane 73 and ethylene glycol. Infra-red analysis of the product revealed a carbonyl peak at 1685 cm^{-1} consistent with the free acid. The ^{1}H NMR spectrum of the product showed a multiplet at 4.11 ppm and a singlet at 5.89 ppm which integrated to 4 and 1 protons respectively. These signals were attributed respectively to the methylene protons at positions 4 and 5 of the dioxolane ring and the methine proton

Scheme 1-4: Planned synthetic approach to compound **67**


OH
OH
CHO
COOH
TsOH
O
O
COOH
SOCl2
COCl
CH2N2
Ag2O
EtOH
+
N
N
O
H
COOEt

73

67

at position 2 of the dioxolane ring. The mass spectrum of the product (parent ion at m/e = 194 major fragments at m/e = 193 corresponding to loss of H$^{\cdot}$ and m/e = 149 corresponding to either subsequent cleavage of the dioxolane ring or to an initial α cleavage of the carboxylic acid group) is consistent with the pattern expected for 73.

The next synthetic step was the formation of a diazoketone, to be used in an Arndt-Eistert reaction. The route to the diazoketone involved initial formation of the acid chloride, followed by treatment of it with diazomethane (35).

Treatment of 2-(4-carboxyphenyl)-1,3-dioxolane 73 with thionyl chloride resulted in ca. 50% loss of the dioxolane ring and the regeneration of some aldehyde in a complex mixture of unrecognizable products (as determined by ^{1}H NMR and TLC, 5% ether in hexanes as eluent, analysis of an aliquot of the reaction mixture which was quenched with methanol). In an attempt to overcome this problem the reaction was repeated in the presence of pyridine (5%), which appeared to have little effect. The reaction was also attempted in the presence of pyridine (5%) at 0°C. However, under these conditions the reaction was incomplete even after long reaction times (ca. 60% conversion after 18 hours). To overcome these problems the aldehyde protecting group was changed from the ethylene acetal to the acetal obtained from 2,2-dimethyl-1,3-propanediol. Acetals derived from this diol

are less susceptible to acidic hydrolysis. This is presumably a result of increased steric hindrance about the acetal.

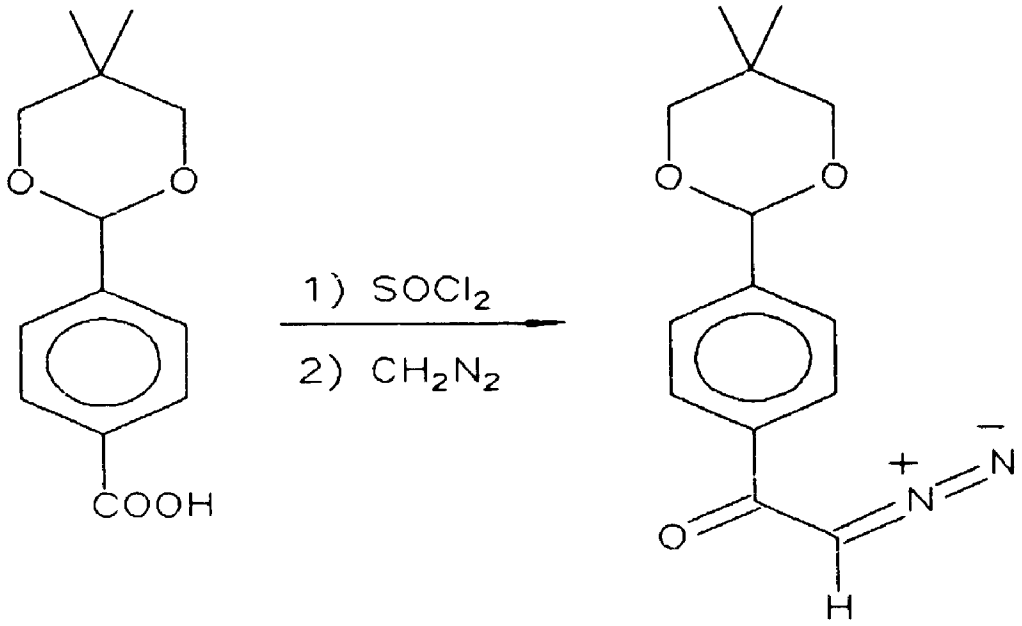
2-(4-Carboxyphenyl)-5,5-dimethyl-1,3-dioxane 74 was prepared in a manner identical to that used for the preparation of 2-(4-carboxyphenyl)-1,3-dioxolane 73. Infrared analysis of the product revealed the carbonyl peak at 1685 cm^{-1}, again consistent with the free acid. The ^{1}H NMR spectrum of the product showed two singlets at 0.82 and 1.30 ppm, each of which integrated to 3 protons, attributable to the axial and equatorial methyl groups on the 5 position of the dioxane ring, two doublets, one at 3.67 ppm, J = 12 Hz, the other at 3.80 ppm, J = 12 Hz, each of which integrated to 2 protons, attributable to the axial and equatorial protons of the methylene groups at positions 4 and 6 of the dioxane ring, and a singlet at 5.45 ppm, which integrated to 1 proton, attributable to the methine proton at position 2 of the dioxane ring. This is consistent with the formation of the desired product. Presumably, this product exists in a preferred conformation in which the phenyl ring occupies an equatorial position. The mass spectrum of the product (parent ion at m/e = 236 and major fragments at m/e = 235 corresponding to loss of $H^{\cdot}$, m/e = 191 corresponding to α cleavage of the carboxylic acid group and m/e = 149 corresponding to cleavage of the dioxane ring) is consistent with the pattern expected for 74.

Treatment of the 2-(4-carboxyphenyl)-5,5-dimethyl-1,3-dioxane 74 with thionyl chloride, even at reflux, did not

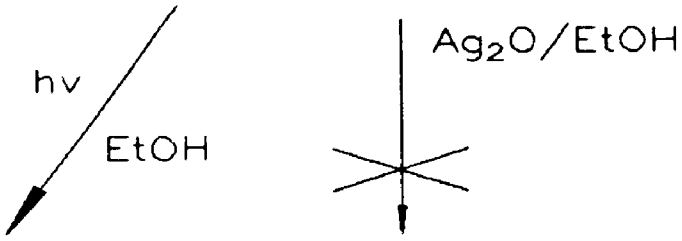
result in any loss of the dioxane ring (as determined by ^{1}H NMR analysis of an aliquot of the reaction mixture which was quenched with methanol). Infrared analysis of this aliquot revealed the presence of only one carbonyl stretch, at 1710 cm^{-1}, consistent with an aryl acid ester. This indicated the desired acid chloride had been formed cleanly. The crude acid chloride was not isolated, but was added to a dilute ethereal solution of diazomethane, after removal of all traces of thionyl chloride. The order of addition was important to minimize formation of undesirable by-products arising from reaction of excess acid chloride with the desired diazoketone (35). Infra-red analysis of the product was consistent with the desired structure 75 and revealed a very strong nitrogen-nitrogen stretch at 2110 cm^{-1} and a carbonyl stretch at 1615 cm^{-1}. The ^{1}H NMR spectrum of the product showed all peaks attributable to the dioxane ring. Also, the ^{1}H NMR spectrum showed a singlet at 5.88 ppm, which integrated to 1 proton. This signal is attributable to the proton of the diazoketone group. The mass spectrum of the product (parent ion at m/e = 260 and fragment at m/e = 219 corresponding to cleavage between the carbonyl and the diazomethyl group) is consistent with the desired product.

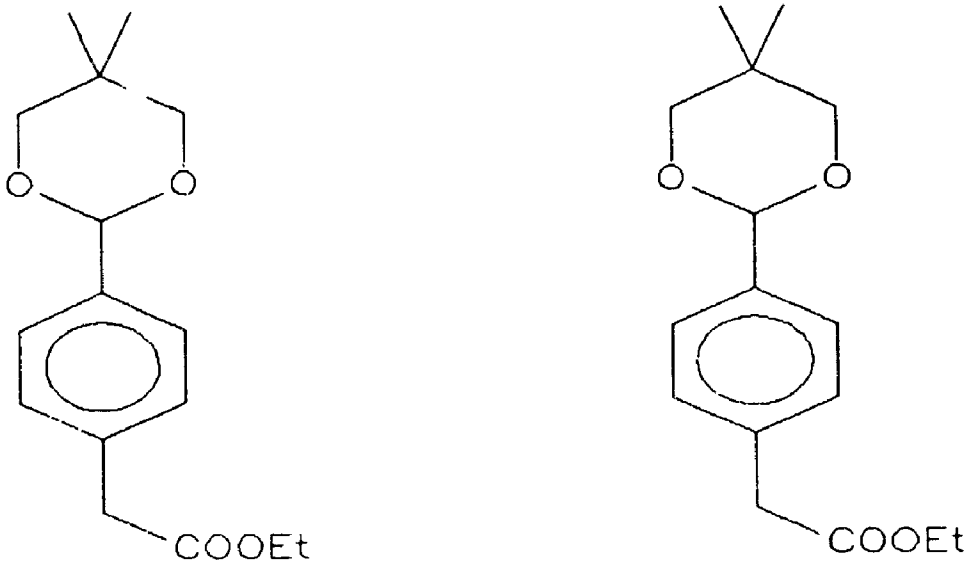
Treatment of 2-(4-diazoacetylphenyl)-5,5-dimethyl-1,3-dioxane 75 with commercial silver oxide did not result in the formation of the desired 2-(4-(carboethoxymethyl)phenyl)-5,5-dimethyl-1,3-dioxane 76, as outlined in Scheme 1-5. Instead,

Scheme 1-5: Synthetic route to compound **76**



74 75





76

the reaction yielded unchanged starting material and small quantities (<10%) of other unidentifiable products. The results of this reaction were improved by using silver oxide freshly prepared by the addition of 20% sodium hydroxide to aqueous silver nitrate. Refluxing the diazoketone 75 in ethanol with the freshly prepared silver oxide resulted in the formation of a yellow oil, which consisted of at least four compounds (as detected by TLC, 5% ether in hexanes as eluent). However, these four compounds could not be separated by either column or preparative thick layer chromatography. Infra-red analysis of the mixture indicated that the desired product may have been formed since a possible ester carbonyl band at 1730 cm^{-1} was observed. As a result of the separation problems encountered with the use of silver oxide as catalyst, it was decided to replace the silver oxide with ultra-violet light irradiation (36).

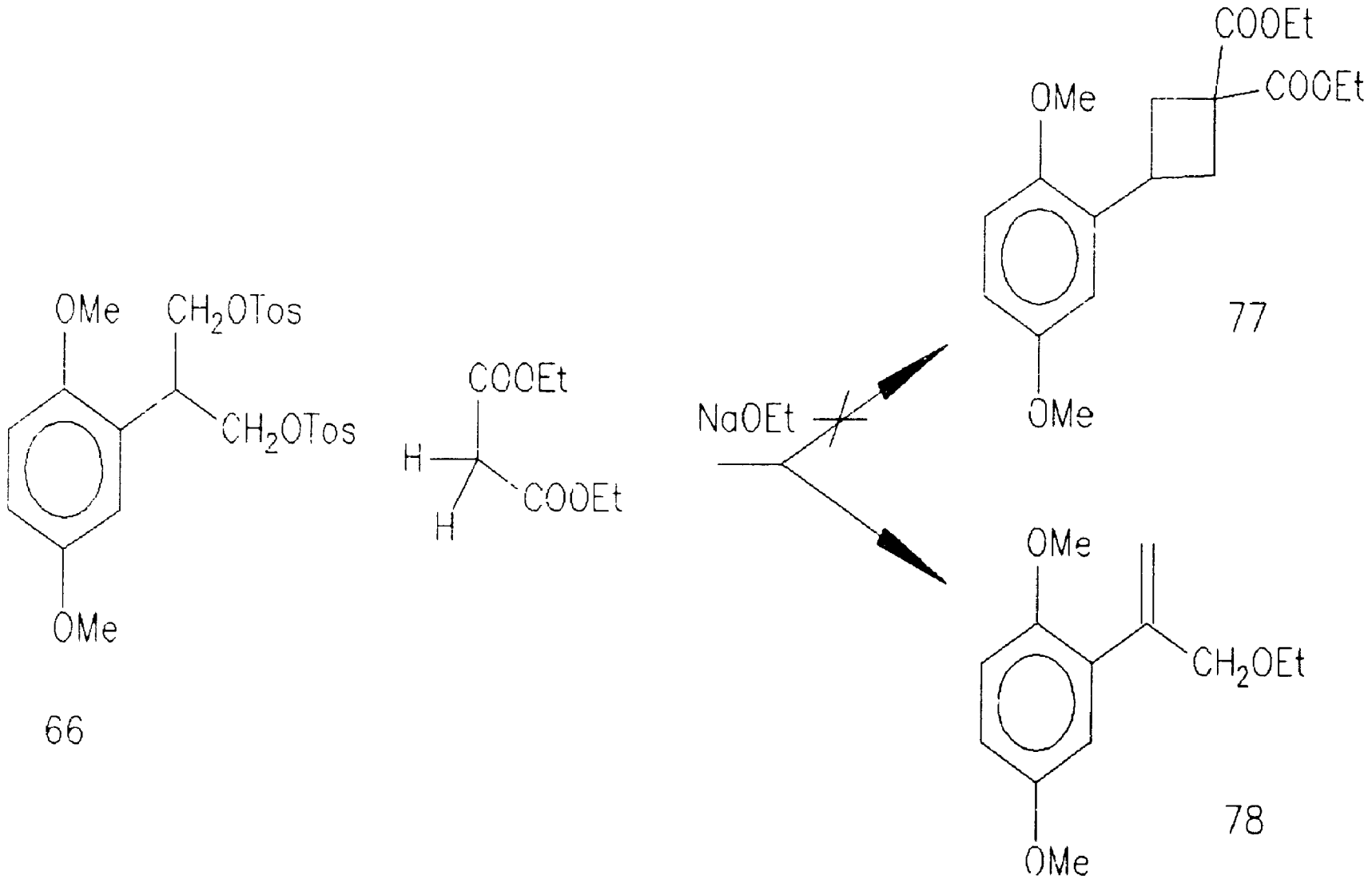
Irradiation of an ethanolic solution of 2-(4-diazoacetylphenyl)-5,5-dimethyl-1,3-dioxane 75 with Pyrex and water filtered light from a medium pressure mercury lamp resulted in the formation of the desired 2-(4-(carboethoxy methyl)phenyl)-5,5-dimethyl-1,3-dioxane 76 in high yield. Infra-red analysis of the product revealed a carbonyl stretch at 1740 cm^{-1} assigned to the ester functionality. The nitrogen-nitrogen stretch formerly seen at 2110 cm^{-1} was absent. The ^1H NMR spectrum showed the absence of the singlet at 5.9 ppm assigned to the proton of the diazoketone group and the appearance of a new singlet at 3.6 ppm, which integrated

to 2 protons, attributable to the benzylic methylene protons. The ^{1}H NMR spectrum also showed the appearance of a quartet at 4.1 ppm, J = 7 Hz, which integrated to 2 protons and a triplet at 1.2 ppm, J = 7 Hz, which integrated to 3 protons; these are assigned to the ethyl group of the ester.

The synthesis of 2-(2,5-dimethoxyphenyl)-1,3-propanediol ditosylate 66 was completed before that of 2-(4-(carboethoxymethyl)phenyl)-5,5-dimethyl-1,3-dioxane 76. While the problems associated with the preparation of 76 were being solved it was decided to investigate the proposed 4-membered ring forming reaction of 66 shown in Scheme 1-1 using diethyl malonate as a model for the activated methylene compound.

Treatment of diethyl malonate with ethanolic sodium ethoxide followed by the addition of 2-(2,5-dimethoxyphenyl)-1,3-propanediol ditosylate 66 resulted in the formation of 2-(2,5-dimethoxyphenyl)-3-ethoxy-propene 78, as outlined in Scheme 1-6. The desired cyclobutane ring containing product 77 was not formed. The propene 78 appears to be obtained from an E2 elimination reaction involving one tosylate and S_N2 substitution of the other by ethoxide. The structure assigned to 78 was determined spectroscopically. The ^{1}H NMR spectrum showed the absence of peaks associated with the tosylate groups and the presence of a multiplet at 4.32 ppm, which integrated to 2 protons. This was assigned to the allylic methylene. Multiplets at 5.26 and 5.43 ppm, each of which integrated to 1 proton, were assigned to the olefinic protons.

Scheme 1-6: Attempted synthesis of compound 77

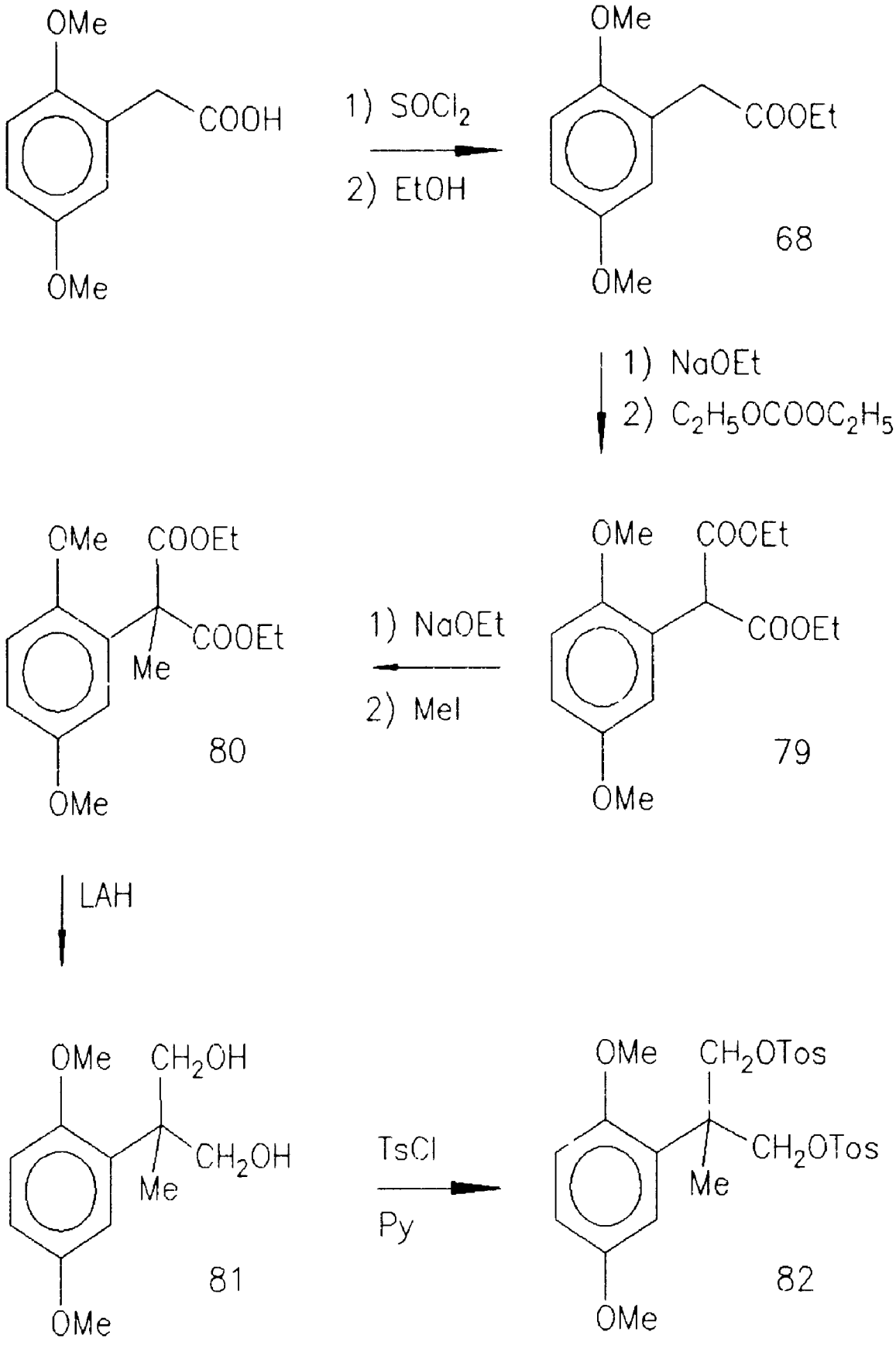

OMe
CH2OTos
CH2OTos
OMe
66
COOEt
H
COOEt
H
NaOEt
COOEt
COOEt
OMe
OMe
77
OMe
CH2OEt
OMe
78

A triplet at 1.18 ppm, which integrated to 3 protons and a quartet at 3.52 ppm, which integrated to 2 protons, were assigned to the ethoxy group.

In an attempt to avoid the elimination reaction the base/solvent conditions were varied. The use of lithium diisopropylamide in tetrahydrofuran resulted in the formation of 2-(2,5-dimethoxyphenyl)-3-tosyloxy-1-propene. Identical results were obtained with the use of potassium hydride in either tetrahydrofuran or dimethylformamide. It was concluded that the malonate was acting as a base and inducing E2 elimination of 66 rather than acting as a nucleophile and so taking part in an S_N2 reaction with 66. It was therefore decided to redesign the synthesis of the ditosylate to incorporate a methyl group at the benzylic position, thereby preventing the elimination reaction. The planned approach to the synthesis of the redesigned ditosylate 82 is outlined in Scheme 1-7.

Ethyl-2,5-dimethoxyphenyl-acetate 68, prepared from the acid as described above, was treated with sodium ethoxide and diethyl carbonate to generate diethyl 2-(2,5-dimethoxyphenyl) malonate 79. Infra-red analysis of the product revealed the expected carbonyl band at 1735 cm^{-1} and a combination band at 1755 cm^{-1}. The ^1H NMR spectrum of the product showed the absence of the singlet at 3.59 ppm, assigned to the benzylic methylene in 68, and the presence of a singlet at 5.08 ppm, which integrated to 1 proton, attributable to the benzylic methine of 79. Also the ^1H NMR spectrum showed that the

Scheme 1-7: Synthetic route to compound **82**


OMe
COOH
OMe
1) $SOCl_2$
2) EtOH
OMe
COOEt
OMe
68
1) NaOEt
2) $C_2H_5OCOOC_2H_5$
OMe
COCEt
COOEt
OMe
79
1) NaOEt
2) MeI
OMe
COOEt
COOEt
Me
OMe
80
LAH
OMe
CH_2OH
CH_2OH
Me
OMe
81
TsCl
Py
OMe
CH_2OTos
CH_2OTos
Me
OMe
82

integrals of the ethyl protons had doubled in size, relative to those of 68. The mass spectrum of the product (parent ion at m/e = 296 and major fragment at m/e = 224 corresponding to a McLafferty rearrangement followed by rapid decarboxylation) is consistent with the expected pattern for 79.

Treatment of diethyl 2-(2,5-dimethoxyphenyl)malonate 79 with sodium ethoxide, to generate the anion, followed by the addition of methyl iodide resulted in the formation of diethyl 2-(2,5-dimethoxyphenyl)-2-methylmalonate 80. The ^{1}H NMR spectrum of the product showed the absence of the singlet at 5.08 ppm, assigned to the benzylic methine of 79, and the appearance of a singlet at 1.8 ppm, which integrated to 3 protons, attributable to the methyl group of 80.

The diethyl 2-(2,5-dimethoxyphenyl)-2-methylmalonate 80 was reduced with lithium aluminum hydride to give 2-(2,5-dimethoxyphenyl)-2-methyl-1,3-propanediol 81. The absence of a carbonyl stretch in the infra-red spectrum and the large band at 3300 cm^{-1} is consistent with the formation of the diol. The ^{1}H NMR spectrum of the product showed two broad doublets, one at 3.85 ppm and the other at 4.17 ppm, these are attributable to the two sets of diastereotopic protons on the methylene carbons at positions 1 and 3 of the propanediol. The mass spectrum of the product (parent ion at m/e = 226) is consistent with the diol 81.

Treatment of the 2-(2,5-dimethoxyphenyl)-2-methyl-1,3-propanediol 81 with p-toluenesulfonyl chloride in pyridine resulted in the formation of 2-(2,5-dimethoxyphenyl)-2-methyl-

1,3-propanediol ditosylate 82. The infra-red spectrum of the product revealed the absence of the O-H stretch at 3300 cm^{-1}. The ^1H NMR spectrum of the product showed a singlet at 2.45 ppm, a doublet at 7.29 ppm, J = 8 Hz, and a doublet at 7.64 ppm, J = 8 Hz. These signals integrated to 6, 4 and 4 protons respectively. This indicated that two tosylate groups had been incorporated into the product, as desired. The mass spectrum of the product (parent ion at m/e = 534 and fragments at m/e = 348 corresponding to loss of methyl tosylate) is consistent with 82.

With the new ditosylate 82 in hand the model study was resumed, again using diethyl malonate as the activated methylene precursor of the cyclobutane.

Treatment of diethyl malonate with lithium diisopropylamide in tetrahydrofuran followed by the addition of 2-(2,5-dimethoxyphenyl)-2-methyl-1,3-propanediol ditosylate 82 yielded principally unreacted starting material and small amounts of tar. The resistance toward nucleophilic attack of compound 82, relative to compound 66, is a result of the structural changes introduced by the addition of the methyl group at carbon 2. While the tosyl groups of compound 66 are bonded to primary carbons, the tosyl groups of compound 82 are bonded to neopentyl type carbon atoms. The relative rate of an S_N2 reaction at a neopentyl center is six and a half orders of magnitude slower than at a primary center (37). Attempts to increase the rate and yield of this reaction by using conditions which enhance the nucleophilic character of the

nucleophile, such as the addition of hexamethylphosphoramide to the lithium diisopropylamide/tetrahydrofuran reaction and the use of potassium hydride in tetrahydrofuran containing the crown ether 18-crown-6, failed to alter the reaction result.

Due to the problems encountered in finding suitable reaction conditions, it was decided to replace the ditosylate 82 with the more easily prepared model compound 2,2-dimethyl-1,3-propanediol ditosylate 83 in further reaction trials. This was done in order to save material.

2,2-Dimethyl-1,3-propanediol ditosylate 83 was prepared by treating 2,2-dimethyl-1,3-propanediol with p-toluenesulfonyl chloride in pyridine. The ^{1}H NMR spectrum of the product showed the presence of a singlet at 2.44 ppm, a doublet at 7.33 ppm, J = 8 Hz, and a doublet at 7.71 ppm, J = 8 Hz. These signals integrated to 6, 4 and 4 protons respectively. This indicated that two tosyl groups were present in the product. The mass spectrum of the product (parent ion at 412 and major fragments at m/e = 155 and 91 corresponding to fission of the sulfur oxygen bond and the sulfur carbon bond respectively) is consistent with compound 83.

Using 2,2-dimethyl-1,3-propanediol ditosylate 83 the model study was resumed, again with the use of diethyl malonate as the activated methylene precursor of the cyclobutane.

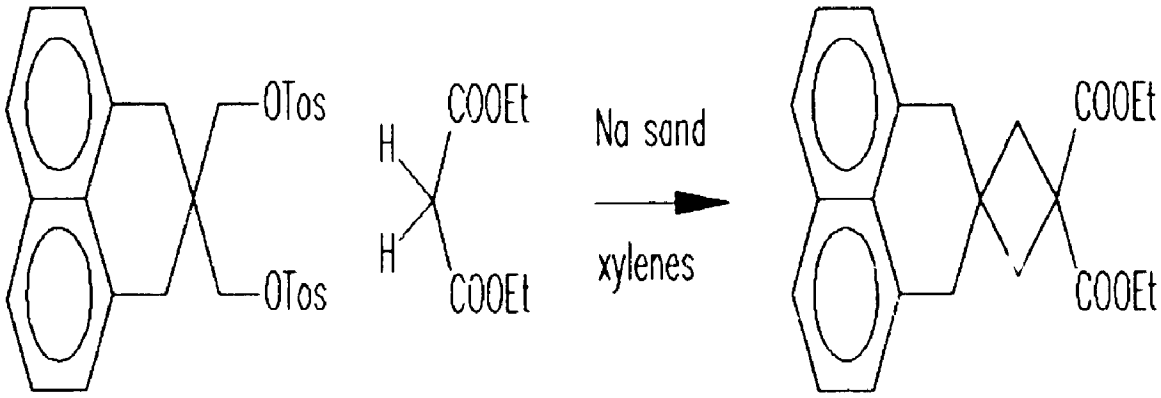
Treatment of diethyl malonate with lithium diisopropylamide in tetrahydrofuran followed by the addition of 2,2-

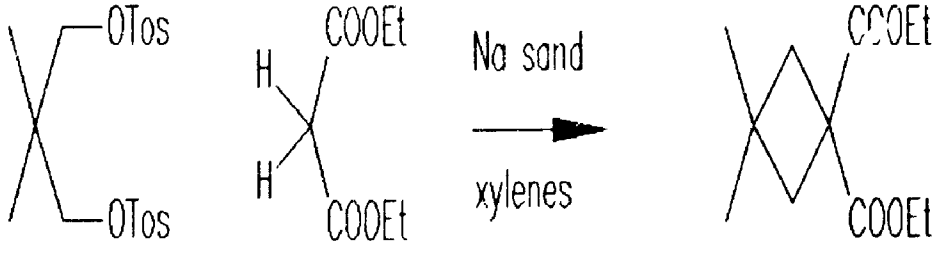
dimethyl-1,3-propanediol ditosylate 83 also yielded principally unreacted starting materials and small amounts of tar. Similar results were again obtained using potassium hydride in tetrahydrofuran containing the crown ether 18-crown-6.

A report by Gerson et al (38) in which sodium sand in refluxing xylenes was used to effect a similar reaction, illustrated in Scheme 1-8, suggested an alternative reagent for the preparation of the precursor to the cyclobutane linked porphyrin quinone species. The model reaction, between 2,2-dimethyl-1,3-propanediol ditosylate 83 and diethyl malonate, was successfully performed using these conditions (Scheme 1-9). The infra-red spectrum of the product revealed the expected carbonyl stretch at 1730 cm^{-1} along with a shoulder peak at 1750 cm^{-1}. The ^{1}H NMR spectrum of the product showed a singlet at 1.09 ppm, which integrated to 6 protons, attributable to the gem dimethyl groups at position 3 of the cyclobutane ring. A singlet which was observed at 2.35 ppm and which integrated to 4 protons is assigned to the methylene protons at positions 2 and 4 of the cyclobutane ring, while a triplet at 1.22 ppm, J = 7 Hz, which integrated to 6 protons, and a quartet at 4.17 ppm, J = 7 Hz, which integrated to 4 protons, are assigned to the ethyl groups of the esters. The mass spectrum of the product, parent ion at m/e = 228 (m/e = 229 is observed as a consequence of using chemical ionization techniques) and fragments at m/e = 183 and 155 corresponding to α cleavage on either side of the ester

Scheme 1-8: Cyclization reaction reported by Gerson et. al. (37)

Scheme 1-9: Synthetic route to compound **84**


OTos
OTos
COOEt
H
H
COOEt
Na sand
xylenes
COOEt
COOEt


OTos
OTos
COOEt
H
H
COOEt
Na sand
xylenes
COOEt
COOEt

83

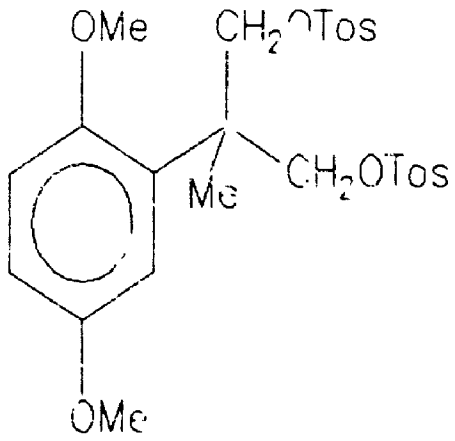
84

carbonyl, is consistent with the expected pattern for compound 84.

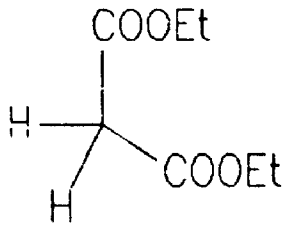
These conditions succeed where others failed probably because of the higher temperatures involved and the fact that the enolate ion is poorly solvated by the non-polar xylenes.

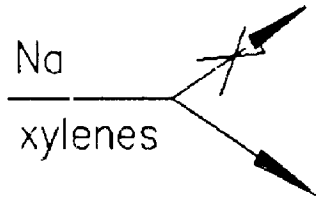
Despite this encouraging result, the use of these conditions on 2-(2,5-dimethoxyphenyl)-2-methyl-1,3-propanediol ditosylate 82 and diethyl malonate did not give the desired cyclobutane. Instead, the malonate anion apparently attacked the methoxy groups on the aromatic ring leading to 86 as the major isolated product via an intramolecular cyclization as illustrated in Scheme 1-10. The ^{1}H NMR spectrum of the product showed the absence of one of the methoxy groups and of one of the tosyl groups. The ^{1}H NMR spectrum of the product also showed a broad singlet at 3.94 ppm, which integrated to 2 protons, assigned to the methylene at position 2 of the coumaran ring. A doublet at 4.08 ppm, J = 10 Hz, and a doublet at 4.41 ppm, J = 10 Hz, which integrated to 1 proton each, were assigned to the diastereotopic protons of the methylene attached to the 3 position of the coumaran ring. The mass spectrum of the product (parent ion at m/e = 348 and major fragment at m/e = 163 corresponding to cleavage of the C-3 exocyclic methylene bond) is consistent with compound 86. The fact that this product was isolated in close to a 50% yield is in agreement with the proposed mechanism, since both methoxy

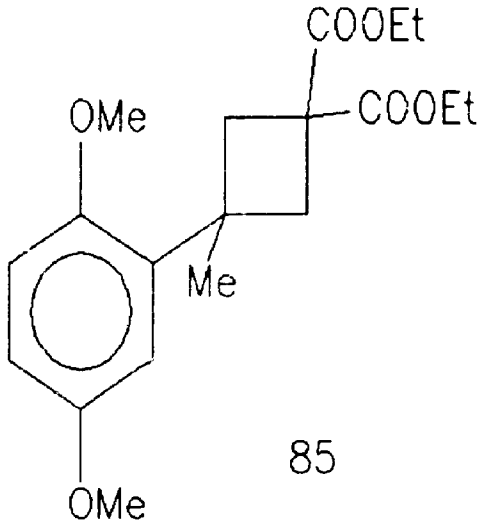
Scheme 1-10: Attempted synthesis of compound **85**


OMe
CH2OTos
Me
CH2OTos
OMe

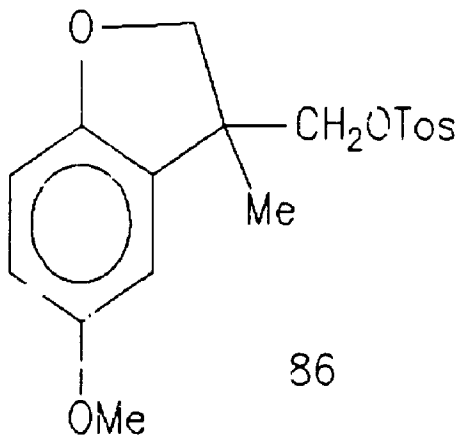
82


COOEt
H
COOEt
H


Na
xylenes


COOEt
COOEt
OMe
Me
OMe

85


O
CH2OTos
Me
OMe

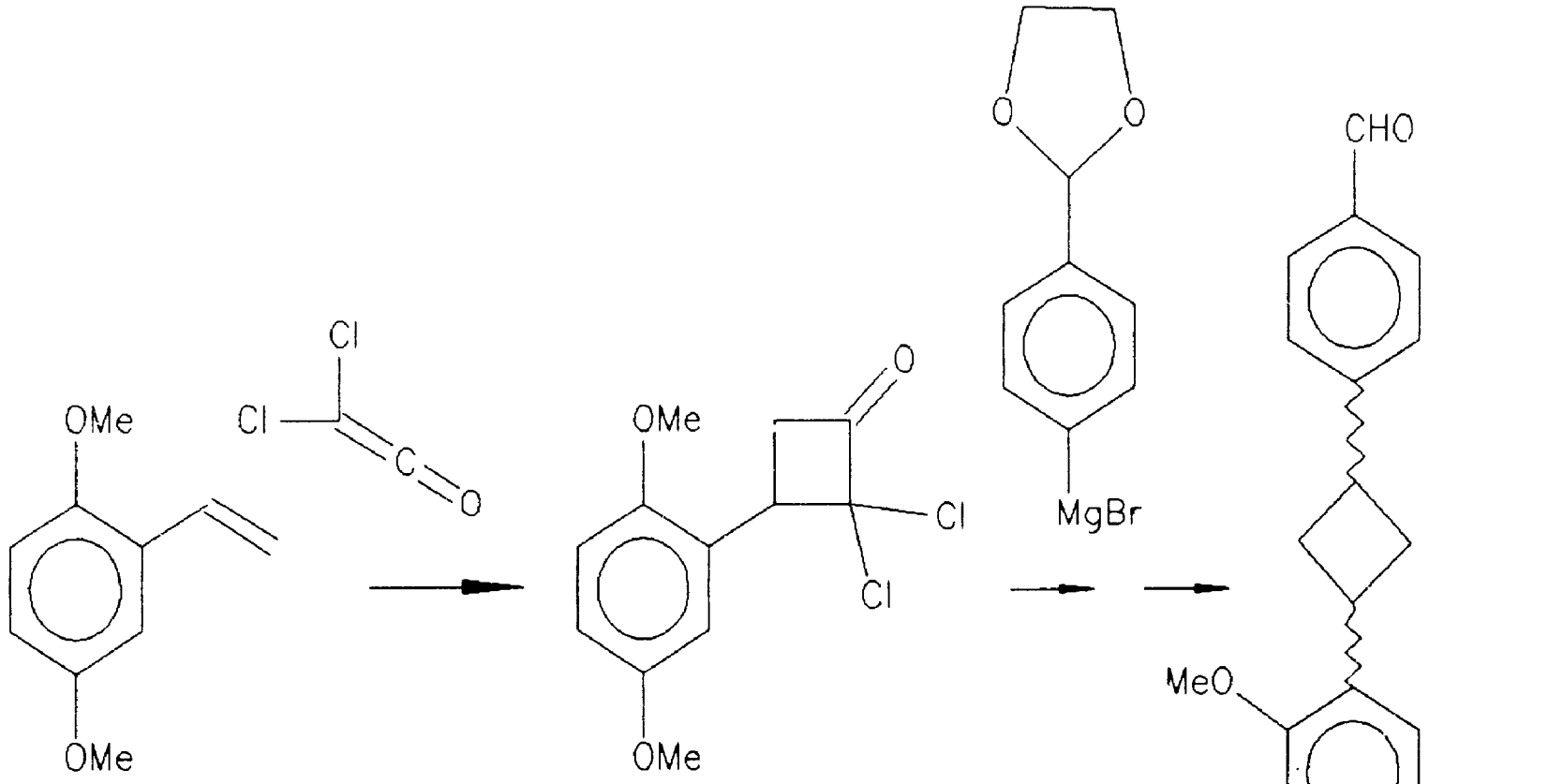
86

groups should be equally likely to be attacked by the malonate anion.

Presumably, the formation of 5-methoxy-3-methyl-3-(p-tolylsulfonylmethyl)coumaran 86 reflects the fact that the tosyl groups of 2-(2,5-dimethoxyphenyl)-2-methyl-1,3-propanediol ditosylate are on neopentyl type carbons, and as such are extremely unreactive in an S_N2 reaction (37). In view of this fatal result, the synthetic approach toward the cyclobutane linked benzaldehyde dimethoxybenzene intermediates 64 and 65 was completely redesigned.

The new approach involved a ketene addition to an appropriately substituted styrene followed by the addition of an appropriately substituted phenyl Grignard to the initially formed cyclobutanone, as outlined in Scheme 1-11. The species initially chosen for this reaction were 2,5-dimethoxystyrene 87 and the Grignard reagent obtained from 2-(4-bromophenyl)-1,3-dioxolane 88. Although ketene itself does not add to styrene, the dichloro analogue does so readily (39). This difference is attributed to stabilization of charge development in the transition state by the chlorine atoms. It was therefore decided to use dichloroketene instead of ketene itself. The dichloroketene addition was expected to yield the desired 2,2-dichloro-3-(2,5-dimethoxyphenyl) cyclobutanone 89 and not the isomeric 2,2-dichloro-4-(2,5-dimethoxyphenyl) cyclobutanone by analogy with the reaction of dichloroketene and styrene (40). The regiochemistry of this reaction is governed by the relative nucleophilicity of

Scheme 1-11: Planned synthetic approach to compounds **64** and **65**



87 89 64 65

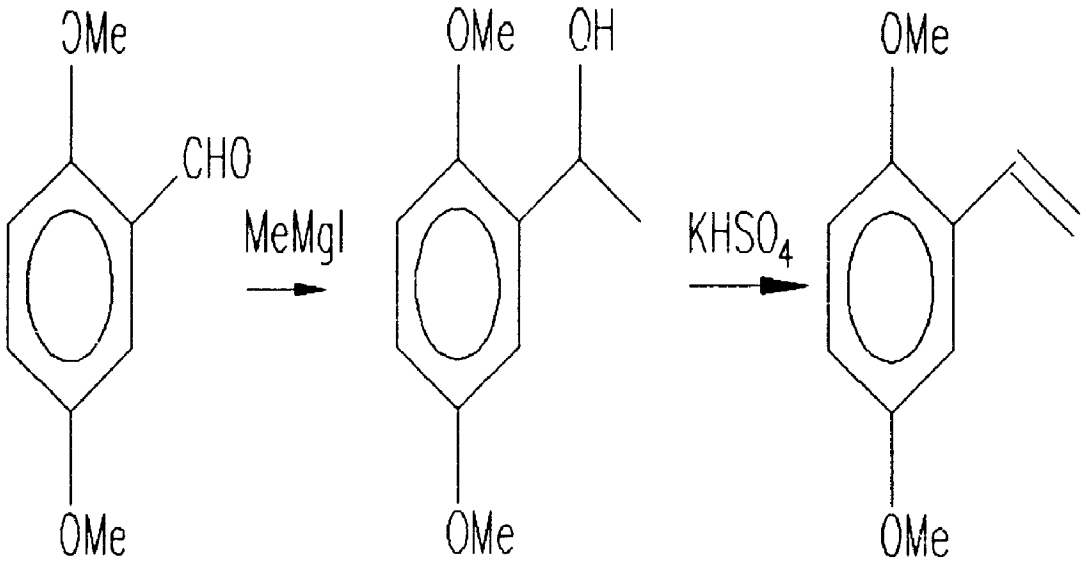
the carbon atoms of the olefin; the more nucleophilic center bonds to the sp hybridized carbon of the ketene (39). Addition of the aryl Grignard to 89 was expected to give a cyclobutanol which could then be converted to a cyclobutyl-chloride by treatment with thionyl chloride. Reductive dehalogenation, which would remove all three chlorine atoms, followed by deprotection of the aldehyde would yield the desired intermediates 64 and 65 shown in Scheme 1-11.

The initial synthetic targets were, therefore, the styrene 87 and the bromophenyl-dioxolane 88. The planned approach to the styrene utilized 2,5-dimethoxybenzaldehyde as the starting material and is outlined in Scheme 1-12.

2,5-Dimethoxybenzaldehyde was added to methyl magnesium iodide to yield 1,4-dimethoxy-2-(1-hydroxyethyl)benzene 90. The absence of a carbonyl band in the infra-red spectrum and the presence of a large band at 3400 cm^{-1} is consistent with formation of the alcohol. The ^1H NMR spectrum of the product showed a doublet at 1.49 ppm, J = 6 Hz, which integrated to 3 protons, and a multiplet at 5.06 ppm which integrated to 1 proton. These signals were assigned respectively to the methyl and the methine of the 1-hydroxyethyl side chain. The mass spectrum of the product (parent ion at m/e = 182 and fragment at m/e = 167 corresponding to loss of a methyl group) is consistent with compound 90.

Adding the 1,4-dimethoxy-2-(1-hydroxyethyl)benzene 90 and a trace of the radical scavenger 2,6-di-t-butyl-p-cresol to fused potassium bisulfate and a trace of 2,6-di-t-butyl-p-

Scheme 1-12: Synthetic route to compound **87**



90 87

cresol held in a 190°C bath and evacuated to 20 mm Hg effected the elimination, to produce 2,5-dimethoxystyrene 87. It was necessary to have the radical scavenger present and to distil the 2,5-dimethoxystyrene from the reaction vessel as it formed to avoid polymerization. This procedure is similar to that used in the synthesis of halogenated styrenes (41). The absence of the O-H stretch in the infra-red spectrum is consistent with the formation of the styrene. The ^{1}H NMR spectrum of the product showed a doublet of doublets at 5.27 ppm, J = 10 and 2 Hz, which integrated to 1 proton assigned to the olefinic proton trans to the 2,5-dimethoxyphenyl ring, a doublet of doublets at 5.72 ppm, J = 18 and 2 Hz, which integrated to 1 proton assigned to the olefinic proton cis to the 2,5-dimethoxyphenyl ring, and a doublet of doublets at 7.03 ppm (superimposed on the aromatic protons), J = 18 and 10 Hz, which increased the size of the integral of the aromatic protons by 1 proton, assigned to the olefinic proton gem to the 2,5-dimethoxyphenyl ring. These peak assignments are in agreement with published data for this compound which has previously been prepared by Mayen and Marechal (42).

The styrene so prepared was found to be contaminated with small amounts of the alcohol precursor as well as the initial starting material, 2,5-dimethoxybenzaldehyde. Any attempt to purify the 2,5-dimethoxystyrene by distillation or by chromatography resulted in considerable losses due to polymerization. The contamination by the aldehyde, was problematical in that it resulted in the formation of

inseparable by-products in the next reaction, the ketene addition. To overcome this it was necessary to pre-treat the styrene with lithium aluminum hydride, thereby reducing the aldehyde to the benzyl alcohol, prior to the ketene addition. It was not necessary to remove either the benzyl alcohol or the 1,4-dimethoxy-2-(1-hydroxyethyl)benzene 90 from the 2,5-dimethoxystyrene 87, as the by-products formed from reaction with these impurities were readily removed by recrystallizing the desired product.

There are two common procedures for generating dichloroketene, which is prepared in situ due to its high reactivity (39). The first involves a reductive dehalogenation by zinc metal of trichloroacetyl chloride. This procedure suffers the disadvantage that the by-product zinc chloride is a Lewis acid which can catalyze the polymerization of styrene (43). To avoid this problem, Krepski and Hassner report the addition of a equimolar amount of phosphorous oxychloride to be effective in suppressing polymerisation of styrene (43). This procedure, however, was not found to prevent the polymerization of the more electron rich 2,5-dimethoxystyrene. Thus the addition of an equimolar amount of trichloro-acetyl chloride and phosphorous oxychloride to a mixture of 2,5-dimethoxystyrene 87 and a zinc-copper couple in ether resulted in the slow polymerization of the styrene with small quantities (<10%, of the desired 2,2-dichloro-3-(2,5-dimethoxyphenyl)cyclobutanone 89 being formed.

The second common method of generating dichlcroketene involves the triethylamine catalyzed dehydrohalogenation of dichloroacetyl chloride. This method is reported to suffer the disadvantage that the by-product, triethylamine hydrochloride, catalyses the decomposition of dichloroketene (43). This method was, however, found to be acceptable for the production of 2,2-dichloro-3-(2,5-dimethoxyphenyl) cyclobutanone 89. A modification of this procedure, using dichloroacetyl bromide, has been used to synthesise 2,2-dichloro-3-phenyl-cyclobutanone (40).

The addition of triethylamine to a refluxing solution of 2,5-dimethoxystyrene 87 and dichloroacetyl chloride in hexanes yielded the desired 2,2-dichloro-3-(2,5-dimethoxyphenyl) cyclobutanone 89 although in poor yield. The infra-red spectrum of the product revealed the expected carbonyl stretch at 1810 cm^{-1}. The ^{1}H NMR spectrum of the product showed a broad doublet at 3.61 ppm, J = 9 Hz, which integrated to 2 protons and was attributed to the methylene protons at position 4 of the cyclobutanone ring. A broad triplet was observed at 4.29 ppm, J = 9 Hz, which integrated to 1 proton and was attributed to the benzylic methine proton at position 3 of the cyclobutanone ring. The fact that these two signals are coupled to each other with a coupling constant of 9 Hz indicates that these protons must be attached to adjacent carbon atoms. This would only be possible if the ketene addition had occurred with the expected regiochemistry. The final confirmation of the structure of the product was

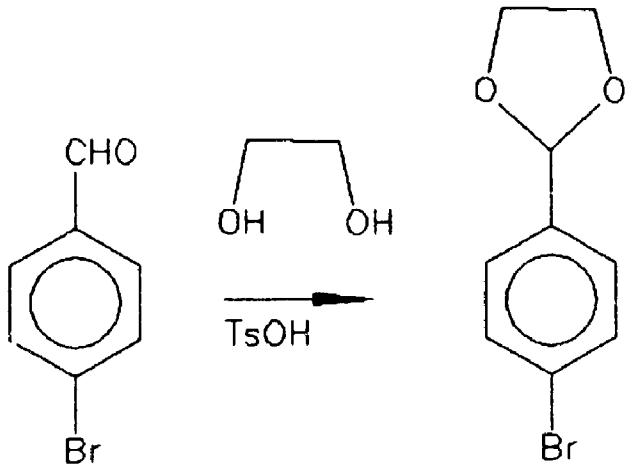
obtained from its mass spectrum which showed the expected molecular ion at m/e = 274 and the major fragment at m/e = 232. This fragment corresponds to a retro 2+2 reaction in which the parent ion losses ketene, again this would only be possible if the dichloro-ketene addition reaction had occurred with the expected regiochemistry.

The next step in the synthesis was the preparation of the dioxolane **88** to be used as a precursor of the Grignard required for reaction with the cyclobutanone **89**. The planned approach to the bromophenyl-dioxolane **88** utilized p-bromobenzaldehyde as the starting material and is outlined in Scheme 1-13.

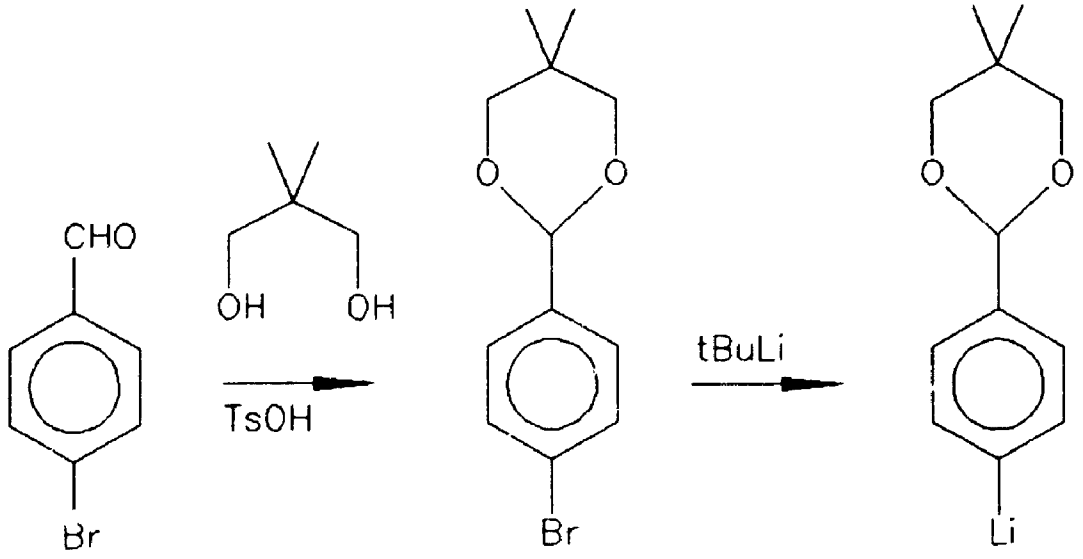
Refluxing p-bromobenzaldehyde with ethylene glycol and a catalytic amount of p-toluenesulfonic acid in dry benzene gave a good yield of 2-(4-bromophenyl)-1,3-dioxolane **88**. The absence of a carbonyl stretch in the infra-red spectrum is consistent with formation of the desired dioxolane. The ^{1}H NMR spectrum of the product showed a multiplet at 4.06 ppm, which integrated to 4 protons, attributable to the methylene protons at positions 4 and 5 of the dioxolane ring, and a singlet at 5.77 ppm, which integrated to 1 proton, attributable to the benzylic methine at position 2 of the dioxolane ring. The mass spectrum of the product (parent ions at m/e = 228, 230 and major fragments at m/e = 227, 229 corresponding to loss of a hydrogen atom and at m/e = 183, 185 corresponding to cleavage of the dioxolane ring) is consistent with compound **88**. The relative intensities of the m/e = 183

Scheme 1-13: Synthetic route to compound **88**

Scheme 1-14: Synthetic route to compound **91**



88



92

91

and 185 peaks was observed to be 50:49, consistent with the isotopic pattern for one bromine atom. This 50:49 ratio was not observed in the m/e = 228, 230 pair of signals due to their relatively weak intensities. The m/e = 227, 229 pair of signals, although intense enough to exhibit this ratio of intensities did not. This is easily explained by the fact that the m/e = 229 signal had several origins: it was formed by loss of a hydrogen atom from a m/e = 230 parent ion, and it was present as one of three possible m+1 isotopic parent ions of m/e = 228. These m+1 isotopic parent ions are the result of the natural abundance of ^{17}O, ^{13}C and ^{2}H.

The synthesis of the 2-(4-bromophenyl)-1,3-dioxolane 88 was completed before that of the 2,2-dichloro-3-(2,5-dimethoxyphenyl)cyclobutanone 89. In order to save time it was decided to optimise the conditions of the Grignard formation and addition using 2-pentanone as a model for the cyclobutanone. This model study was also carried out because there was concern that the aryl dioxolane ring might not be stable to the Grignard reagent.

Although there are examples in the literature of acetal substituted Grignard reagents (44), it was found to be not possible to generate the Grignard reagent from 2-(4-bromophenyl)-1,3-dioxolane 88 in high yield. The yield of Grignard reagent was determined by quenching the Grignard solution with deuterium oxide and measuring the yield of 2-(4-deuterophenyl)-1,3-dioxolane produced. It was, however, found to be possible to generate the aryl lithium reagent in a greater

yield by metal halogen exchange using t-butyl lithium, again as measured by the yield of 2-(4-deuterophenyl)-1,3-dioxolane produced from quenching the reaction mixture with deuterium oxide.

Addition of t-butyl lithium to the 2-(4-bromophenyl)-1,3-dioxolane 88 yielded the phenyl lithium reagent, which was trapped with deuterium oxide. However, the product was contaminated with large quantities (ca. 60%) of the benzaldehyde. This benzaldehyde is likely the result of nucleophilic attack on C-4 of the dioxolane ring by t-butyl lithium. Since the presence of free aldehyde groups is potentially problematical, it was decided to change the aldehyde protecting group from the ethylene acetal to the acetal obtained from 2,2-dimethyl-1,3-propanediol. It was anticipated that this acetal would be more stable to the lithiation conditions.

The planned approach to the 2-(4-lithiophenyl)-5,5-dimethyl-1,3-dioxane 91 also utilized p-bromobenzaldehyde as starting material and is outlined in Scheme 1-14.

The 2-(4-bromophenyl)-5,5-dimethyl-1,3-dioxane 92 was prepared in a manner analogous to that used to prepare 2-(4-bromophenyl)-1,3-dioxolane 88. The absence of a carbonyl stretch in the infra-red spectrum of the product is consistent with the formation of the dioxane. The ^{1}H NMR spectrum of the product showed two singlets at 0.79 and 1.27 ppm, which integrated to 3 protons each and were assigned to the axial and equatorial methyl groups at position 5 of the dioxane

ring. Doublets at 3.63 ppm, J = 11 Hz, and 3.76 ppm, J = 11 Hz, which integrated to 2 protons each were assigned to the axial and equatorial protons of the methylene groups at positions 4 and 6 of the dioxane ring. A singlet at 5.34 ppm, which integrated to 1 proto , was attributed to the benzylic methine at position 2 of the dioxane ring. As with the 2-(4-carboxyphenyl)-5,5-dimethyl-1,3-dioxane 74, the dioxane ring presumably has a preferred conformation in which the phenyl ring is equatorial. The mass spectrum of the product (parent ions at m/e = 270, 272 and major fragments at m/e = 269, 271 corresponding to loss of a hydrogen atom and at m/e = 183, 185, 187 corresponding to two different modes of cleavage of the dioxane ring) is consistent with compound 92. The ratio of the intensities of the parent ion peaks at m/e = 270, 272 are in the expected 50:49 ratio. This 50:49 ratio of intensities is not seen for the peaks at m/e = 269, 271 due to the presence of m+1 isotopic parent ion peaks, as was observed for compound 88. The peaks at m/e = 183, 185, and 187 are actually two sets of isotopic peaks, one at m/e = 183 and 185 and the other at m/e = 185, 187. This analysis is consistent with the observed relative intensities of these three peaks and the expected 50:49 ratio.

The addition of t-butyl lithium to the 2-(4-bromophenyl)-5,5-dimethyl-1,3-dioxane 92 generated the phenyl lithium reagent, which was cleanly trapped with deuterium oxide or 2-pentanone. The ^{1}H NMR spectrum of the product, 93,

obtained from trapping the phenyl lithium with 2-pentanone, showed a triplet at 0.82 ppm which integrated to 3 protons, a multiplet at 1.15 ppm which integrated to 2 protons and a multiplet at 1.74 ppm which integrated to 2 protons. These signals were assigned to the protons on carbons 3, 4 and 5 of the former 2-pentanone. A singlet at 1.50 ppm which integrated to 3 protons was assigned to the protons on carbon 1 of the former 2-pentanone. The mass spectrum of the product (parent ion + H$^{\bullet}$ (due to chemical ionization) at m/e = 279 and fragment at m/e = 261 corresponding to loss of water) is consistent with compound **93**.

The conditions for the lithiation of the 2-(4-bromophenyl)-5,5-dimethyl-1,3-dioxane **92** were thereby established.

The synthesis of the 2,2-dichloro-3-(2,5-dimethoxyphenyl)cyclobutanone **89** was completed before the conditions of the lithiation reaction of **92** were established. Consequently it was decided to determine the likely conditions for the addition of the lithium derivative of **92** to the cyclobutanone **89** using methyl lithium as a model for the aryl lithium. Phenyl lithium would have been a better model; however, methyl lithium was used because of its greater availability.

The addition of methyl lithium to 2,2-dichloro-3-(2,5-dimethoxyphenyl)cyclobutanone **89** resulted in a complex mixture of products and a large amount of unchanged starting material. Due to the complex nature of the product mixture, its ^{1}H NMR spectrum was of limited value in determining the reaction

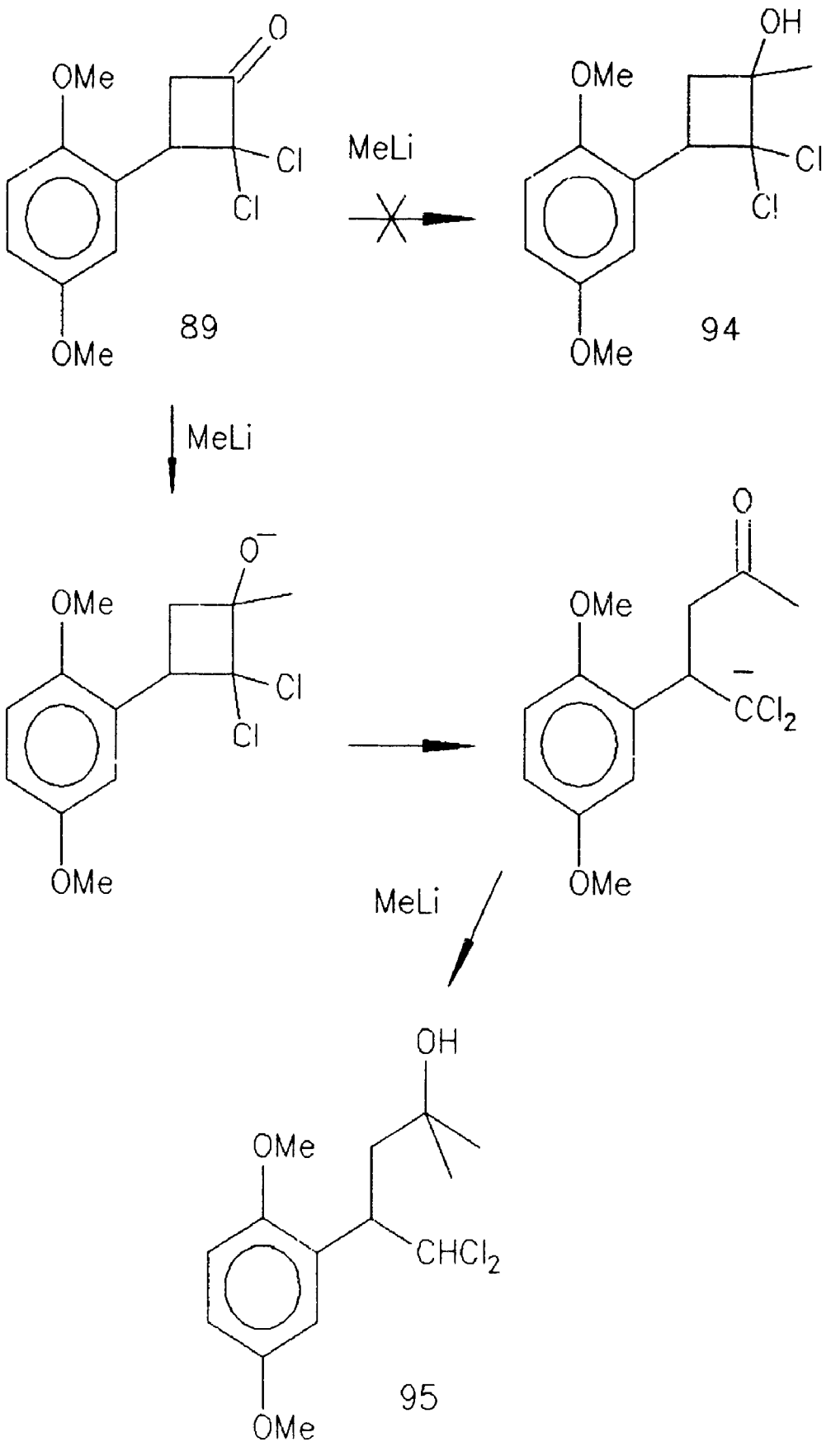
outcome. GC-MS analysis of the product mixture did however reveal that the major product had a parent ion at m/e = 306, which would correspond to the addition of two equivalents of methyl lithium. A reasonable structure for this product, **95**, requires opening of the cyclobutanone ring, as illustrated in Scheme 1-15. This ring opening reaction is analogous to the final steps of the iodoform reaction. The ring opening presumably proceeds, even though only two chlorine atoms are present to stabilize the resulting carbanion, due to the release of ring strain associated with this C-C bond cleavage.

In an attempt to avoid this complex mixture of products, including those involving ring opening, it was decided to dechlorinate the 2,2-dichloro-3-(2,5-dimethoxyphenyl)-cyclobutanone prior to the organo lithium addition.

Due to the acid sensitive nature of the aryl methyl ether groups in **89**, neutral or basic reaction conditions were required for the dechlorination. The most common method of reductive dehalogenation of alkyl halides to hydrocarbons in neutral or basic media is free radical reduction with tributyl tin hydride (45). However, addition of the radical initiator azobisisobutyronitrile, AIBN, to a refluxing solution of the dichlorocyclobutanone **89** and tributyl tin hydride in ether did not effect the desired reaction. This reaction mixture yielded unchanged starting material and unidentified tar.

The reported use of zinc and acetic acid to effect the reduction of 2,2-dichloro-3-(4-methoxyphenyl)cyclobutanone to 3-(4-methoxyphenyl)cyclobutanone (46) suggested that this

Scheme 1-15: Attempted synthesis of compound **94**


OMe
O
Cl
Cl
OMe
89
MeLi
OMe
OH
Cl
Cl
OMe
94
MeLi
OMe
O⁻
Cl
Cl
OMe
OMe
O
OMe
CCl2
OMe
MeLi
OH
OMe
CHCl2
OMe
95

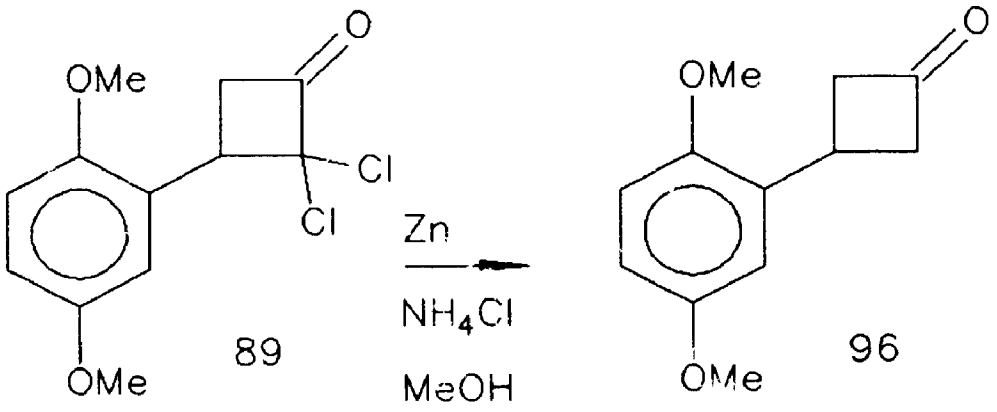
reagent might be mild enough to use on the dimethoxyphenyl analog 89 without inducing demethylation of the aryl methyl ether functions. The application of this reagent to 2,2-dichloro-3-(2,5-dimethoxyphenyl)cyclobutanone 89 resulted in the formation of a 3:2 mixture of compounds after 48 hours reaction. The minor component of this mixture was the desired 3-(2,5-dimethoxyphenyl)cyclobutanone 96 while the major component was the product of replacement of a single chlorine atom by hydrogen in 89.

A report of the use of zinc and ammonium chloride in methanol as a general reagent to effect the reduction of dichlorocyclobutanones to cyclobutanones (47) suggested an alternative and possibly more reactive reagent. In fact this reagent quickly and cleanly converted the dichloro cyclobutanone 89 into the desired 3-(2,5-dimethoxyphenyl) cyclobutanone 96. The structure of the product was confirmed by infra-red analysis, which revealed a carbonyl stretch at 1785 cm^{-1}. The ^{1}H NMR spectrum of the product showed a multiplet at 3.27 ppm which integrated to 4 protons assigned to the methylene protons of the cyclobutanone ring and a quintet at 3.64 ppm which integrated to 1 proton assigned to the benzylic methine. The mass spectrum of the product (parent ion at m/e = 206 and major fragment at m/e = 164 corresponding to retro 2+2 ring opening with the associated loss of ketene) is consistent with compound 96.

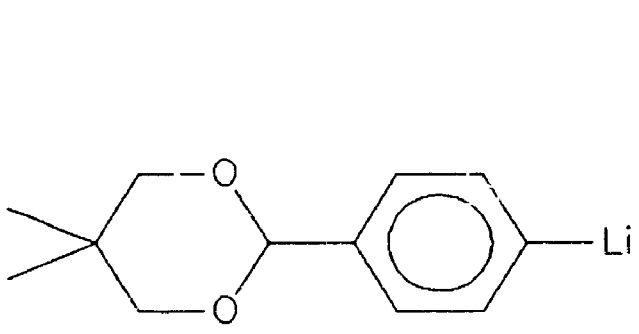
The addition of 3-(2,5-dimethoxyphenyl)cyclobutanone 96 to a tetrahydrofuran solution of the phenyl lithium species

91 resulted in the formation of the desired alcohol 97, as outlined in Scheme 1-16. Although this product may be formed as a mixture of both cis and trans isomers no attempt was made to separate them. The major component did however crystallize and was obtained in pure form. The infra-red spectrum of the major product revealed an O-H stretch at 3460 cm^{-1}, which may imply that it has the aromatic rings in a trans relationship. This would allow for an intramolecular hydrogen bond between the alcohol group and the ether oxygen attached to the 2-position of the dimethoxyphenyl ring. This hydrogen bond would explain the relatively low energy stretching frequency observed for the product O-H bond (48). The ^1H NMR spectrum of the product showed the anticipated signals with consistent chemical shifts and coupling patterns. Thus two singlets at 0.79 and 1.29 ppm which integrated to 3 protons each were seen and assigned to the methyl groups on position 4 of the dioxane ring. An exchangeable, very broad signal at ca. 2.1 ppm which integrated to 1 proton was assigned to the hydroxyl proton, and two multiplets at 2.47 and 2.96 ppm which integrated to 2 protons each were assigned to the prochiral methylene protons of the cyclobutane ring. A multiplet at 3.21 ppm which integrated to 1 proton was attributed to the benzylic methine of the cyclobutane ring, and two doublets at 3.65 ppm, J = 12 Hz, and 3.77 ppm, J = 12 Hz, which integrated to 2 protons each were assigned to the methylene protons at positions 3 and 5 of the dioxane ring. Two singlets at 3.71 and 3.77 ppm which integrated to 3 protons each are assigned

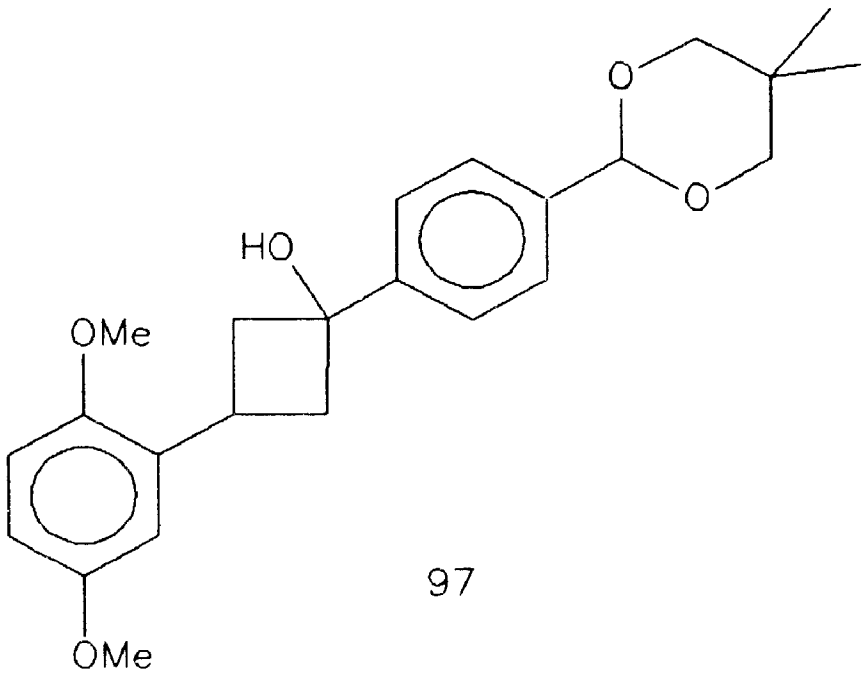
Scheme 1-16: Synthetic route to compound **97**



89 96



91



97

to the protons of the methoxy groups, a singlet at 5.41 ppm which integrated to 1 proton was assigned to the benzylic methine of the dioxane ring. A doublet of doublets at 6.67 ppm, J = 10 and 3 Hz, a doublet at 6.73 ppm, J = 10 Hz, and a doublet at 6.86 ppm, J = 3 Hz, each of which integrated to 1 proton are assigned to the aromatic ring protons of the dimethoxyphenyl ring. Doublets at 7.55 ppm, J = 8 Hz, and 7.64 ppm, J = 8 Hz, which integrated to 2 protons each are assigned to the aromatic ring protons of the former phenyl lithium reagent. The ^{13}C NMR spectrum of the product was consistent with compound 97. By comparison of the observed chemical shifts with predicted values, and inspection of the DEPT ^{13}C NMR spectrum, and the ^{1}H-^{13}C heteronuclear correlation spectrum the following peak assignments were made: the methyl carbons at position 5 of the dioxane ring were assigned to two signals at 21.9 and 23.1 ppm. The signal at 25.1 ppm was assigned to the benzylic methine carbon of the cyclobutane ring. The quaternary carbon at position 5 of the dioxane ring was assigned the signal at 30.3 ppm. The methylene carbons of the cyclobutane ring were assigned to the signal at 43.6 ppm. The methyl carbons of the two methoxy groups were assigned to signals at 55.8 and 55.9 ppm. The signal at 72.7 ppm was assigned the quaternary carbon of the cyclobutane ring. The methylene carbons at positions 4 and 6 of the dioxane ring were assigned to the signal at 77.7 ppm. The benzylic methine carbon of the dioxane ring was assigned

to the signal at 101.5 ppm. Signals at 110.8, 111.1, and 113.8 ppm were assigned to the dimethoxy phenyl ring carbons bearing the protons. The former phenyl lithium reagent aromatic ring carbons bearing protons were assigned to signals at 125.6 and 126.4 ppm. The dimethoxy phenyl ring carbon bonded to the cyclobutane ring was assigned to the signal at 134.0 ppm. Two signals at 137.8 and 146.2 ppm were assigned to the former phenyl lithium reagent aromatic ring carbons bonded to the cyclobutane and to the dioxane rings. The dimethoxyphenyl ring carbons bonded to the methoxy groups were assigned to the signals at 151.8 and 153.7 ppm. The mass spectrum of the product (parent ion at m/e = 398 and fragments at m/e = 164 and 233 corresponding to the two fragments resulting from a retro 2+2 ring opening of the cyclobutane ring) is consistent with compound 97. The larger fragment from ring opening of the cyclobutane ring has a m/e ratio of 233 and not 234 due to the rapid loss of a hydrogen atom previously observed to be associated with ionization of the aromatic ring bonded to the dioxane ring. The disproportionate ratio of intensity of the m/e = 164 and m/e = 233 signals is a reflection of the relative ease of ionizing the electron rich dimethoxyphenyl ring.

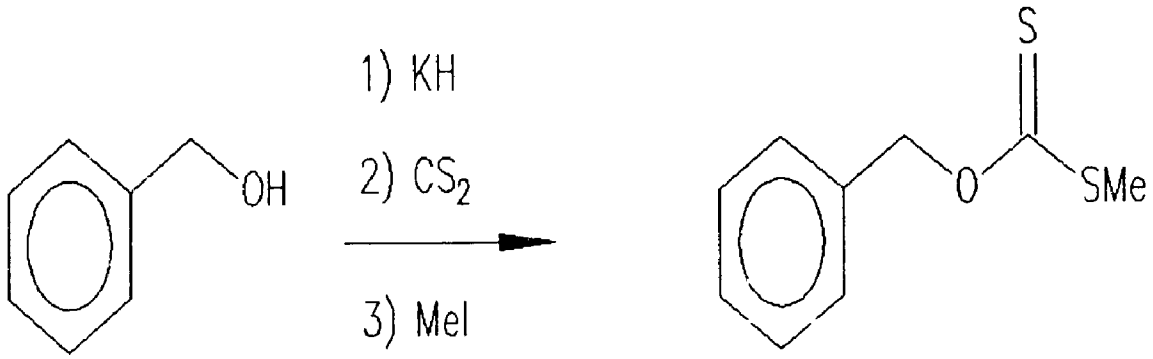
With the alcohol 97 in hand, it remained to remove the hydroxyl group and deprotect the aldehyde to yield the desired intermediates 64 and 65.

There are two well described methods for removing an alcohol functionality. The first involves converting the alcohol to the S-methyl xanthate, by sequential treatment of the alkoxide salt with carbon disulfide and methyl iodide. The S-methyl xanthate is then reduced in a free radical reaction to yield the desired hydrocarbon. This method was initially selected due to the relatively mild conditions employed which should not affect the acid sensitive acetal and methyl aryl ether functionalities present in 97.

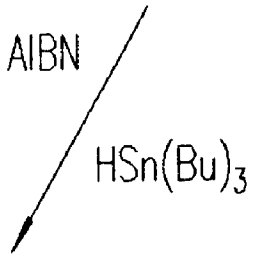
Due to the limited quantity of the alcohol 97 available, it was decided to test this route using benzyl alcohol as a model. Sequential treatment of a solution of benzyl alcohol in tetrahydrofuran at -78°C with potassium hydride, carbon disulfide, and methyl iodide yielded a pale yellow oil. GLC analysis indicated the product to be ca. 80% pure. ^{1}H NMR analysis of the product was consistent with the major component being the desired xanthate 98 (Scheme 1-17). Treatment of the crude xanthate with tributyl tin hydride, prepared from tributyl tin chloride and sodium borohydride (49), and 2,2'-azobisisobutyronitrile yielded toluene. This was confirmed by GLC analysis.

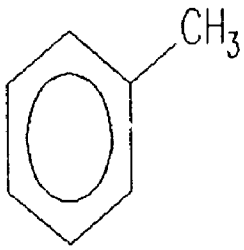
The use of identical conditions to form the S-methyl xanthate 99 derived from alcohol 97 yielded a mixture of starting material, the elimination product 100 (Scheme 1-18), and a number of minor unidentified species. The formation of 100 was unexpected and the evidence for its structure will be discussed further below.

Scheme 1-17: Synthesis of toluene from benzyl alcohol, via compound **98**

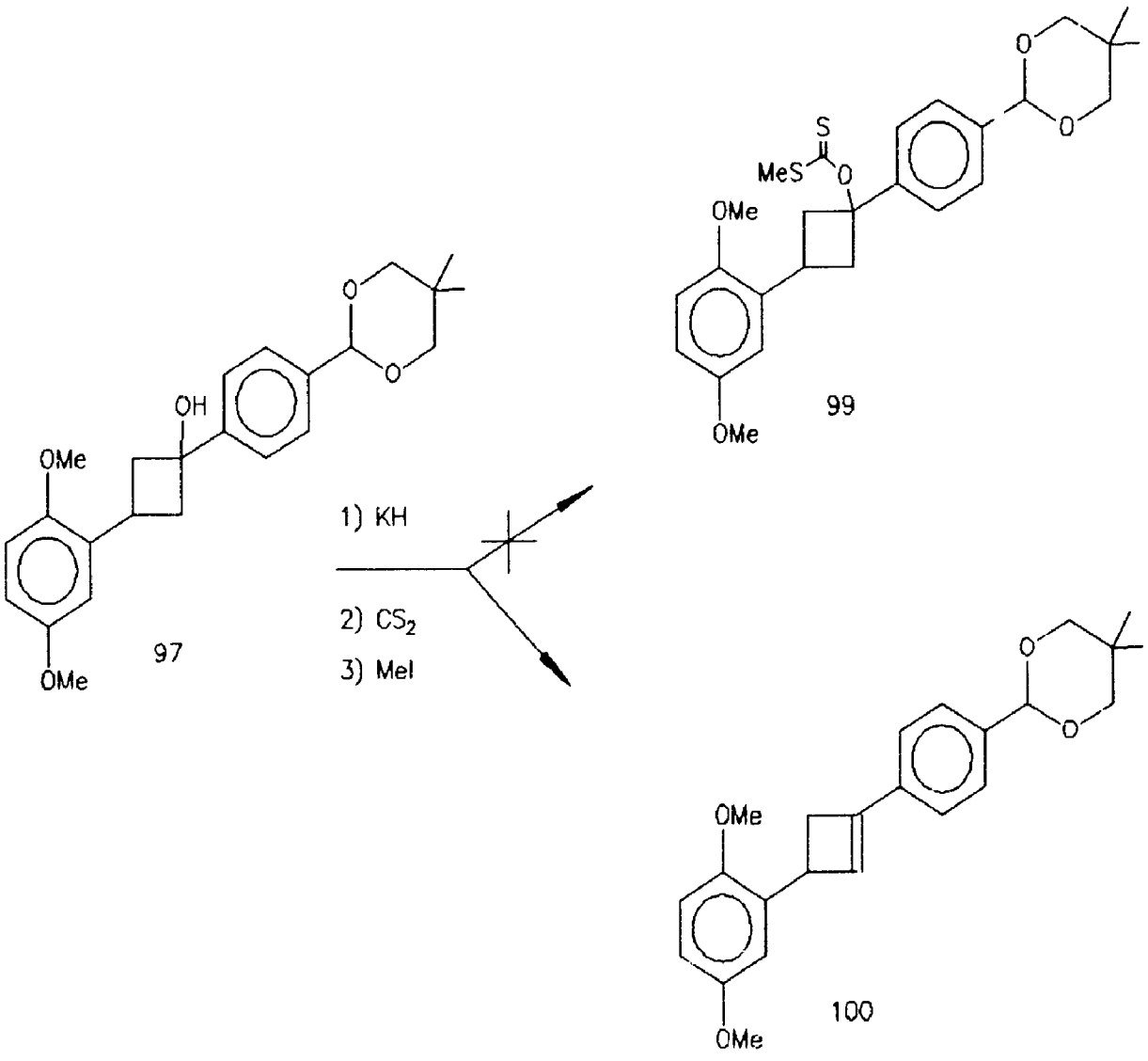


98



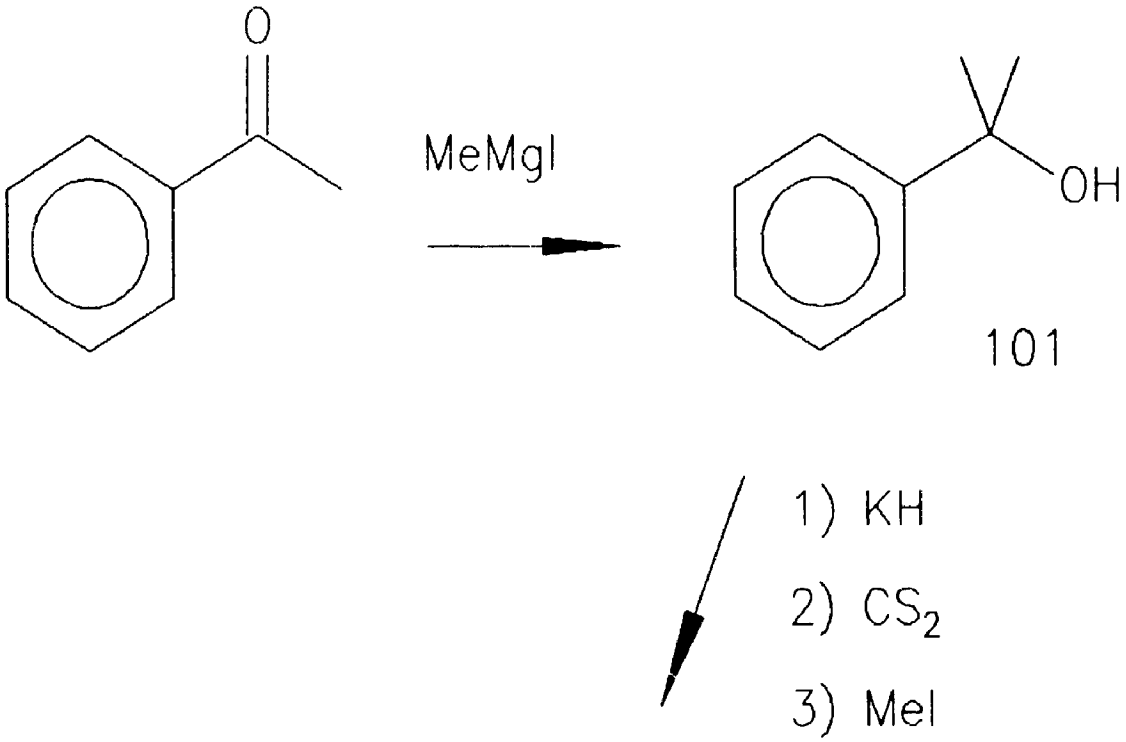


Scheme 1-18: Attempted synthesis of compound **99**


OH
OMe
OMe
97
1) KH
2) CS_2
3) MeI
S
MeS
O
OMe
OMe
99
OMe
OMe
100

The failure of 97 to give the desired xanthate implied that benzyl alcohol was not a good model for the reductive dehydroxylation of 97. 2-Phenyl-2-propanol 101 (Scheme 1-19), derived from the addition of methyl Grignard to acetophenone, proved to be a better model for alcohol 97. Sequential treatment of 101 with hydride, carbon disulfide, and methyl iodide yielded a mixture of starting material, the desired xanthate 102, α-methyl styrene 103, the thio ether 104, and dimethyl trithiocarbonate 105, as outlined in Scheme 1-19. These products were identified by GC-MS. That the α-methyl styrene is derived from the xanthate was proved by repeating the reaction in the absence of carbon disulfide and methyl iodide. Under these conditions only starting material was recovered. The instability of the xanthates derived from alcohols 97 and 101 is presumably due to a facile E1 elimination reaction. Cleavage of the O-C bond results in a relatively stable tertiary benzylic carbocation and the S-methyldithiocarbonate anion. Deprotonation of the carbocation would form the observed α-methyl styrene 103. Decomposition of the anion would yield OCS, a low boiling gas, and methyl thiolate. The methyl thiolate ion may combine with the carbocation to give the thio ether 104 or it may attack another molecule of xanthate resulting in the formation of dimethyl trithiocarbonate 105 and liberating starting alcohol 101. The formation of these side products indicated that the xanthate method for removal of the alcohol functionality would

Scheme 1-19: Attempted synthesis of compound **102**


O
MeMgI
OH
101
1) KH
2) CS_2
3) MeI
S
O
SMe
102
minor
103
major
SMe
104
minor
S
MeS
SMe
105
minor

not be suitable for the preparation of 106 and 107 (Scheme 1-20) from 97.

The second common method for removing an alcohol functionality is to convert it to a halide, usually the chloride, by treatment with an inorganic acid halide. The common reagent for this conversion is either thionyl chloride or phosphorous pentachloride. The halogen is then reduced off, again in a free radical reaction, to yield the desired hydrocarbon.

Due to the fact that benzyl alcohol had been found to be a poor model for alcohol 97 and because the chloride product from reaction of 2-phenyl-2-propanol 101 with thionyl chloride is not expected to be stable, it was decided to attempt these reactions directly on alcohol 97 without benefit of a model study. Treatment of alcohol 97 with thionyl chloride at room temperature yielded starting material and trace amounts of several unidentified products. Heating this reaction mixture gave low yields of the elimination product 100 and of products derived from acetal hydrolysis, as identified by GC-MS and ^{1}H NMR analysis.

Replacing thionyl chloride with phosphorous pentachloride and lowering the reaction temperature to -10°C had only minimal effect on the product composition. Products derived from acetal hydrolysis were still present, as detected by GC-MS and ^{1}H NMR analysis.

In both the thionyl chloride and phosphorous pentachloride reaction trials no single product accounted for

more than 25% of the total product mass. Therefore it was decided to abandon the halide methods for removal of the alcohol functionality.

Both the xanthate and halide routes for reductive dehydroxylation of 97 resulted in the elimination product 100 being formed and in the former reaction the yield of 100 was quite good. Since the alcohol 97 was the product of a long synthesis and hence its supply limited, it was decided to abandon further attempts to convert 97 to 106 and 107 directly and instead to proceed via the cyclobutene 100. Hydrogenation of the double bond of 100 would presumably yield species 106, the cis isomer. It was expected that the cis isomer would be formed because the dimethoxyphenyl ring would block approach of the catalyst to one side of the double bond. This route was, unfortunately, not expected to yield species 107, the trans isomer.

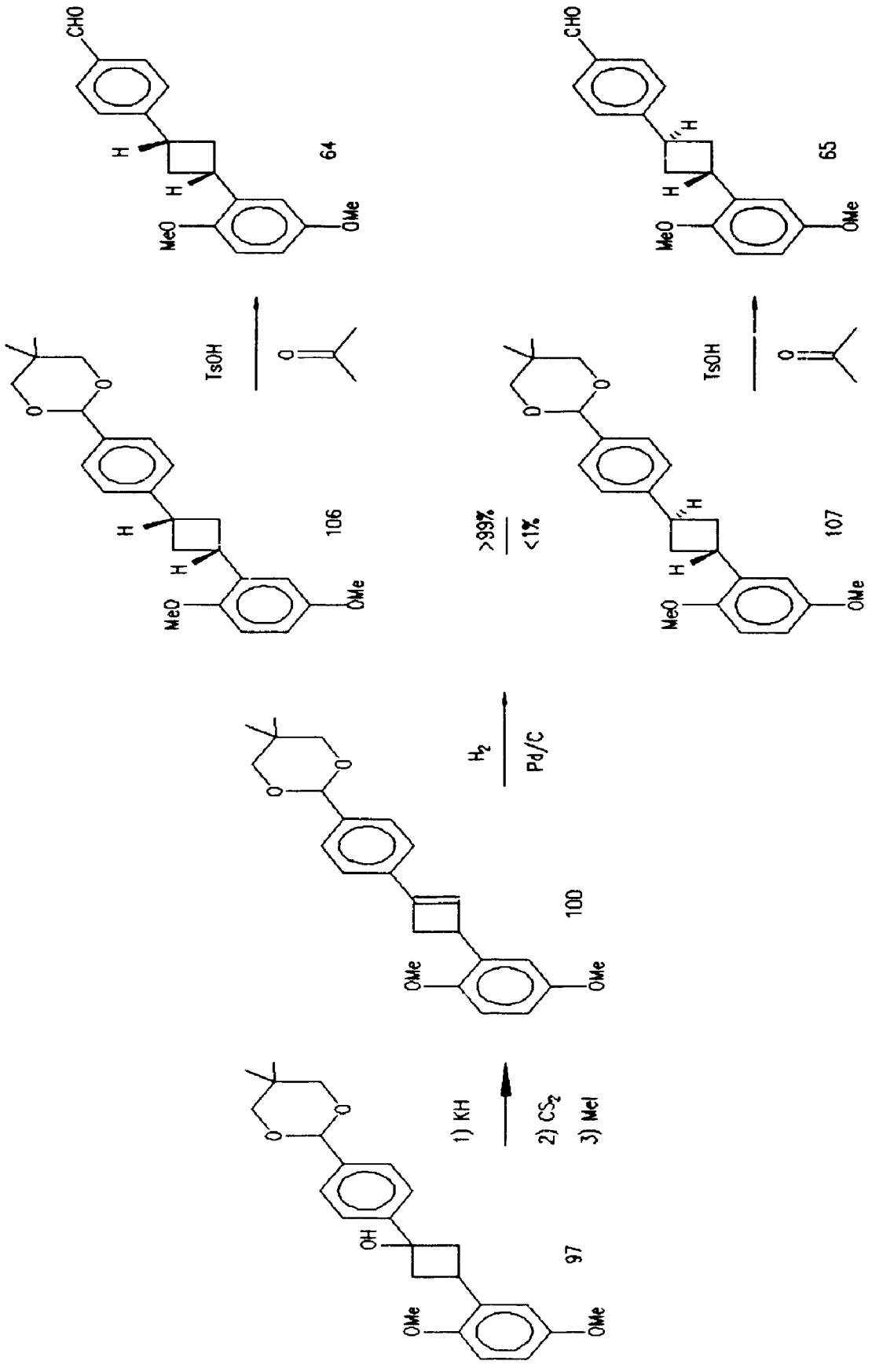
In an attempt to increase the yield of the cyclobutene 100 from the alcohol 97, an acid catalyzed dehydration was performed. These conditions resulted in rapid decomposition to many products. An attempt to prepare the tosylate of alcohol 97, again with the aim of enhancing the yield of cyclobutene, failed. The alcohol proved resistant to treatment with tosyl chloride in pyridine.

In light of the preceding discussion it was decided to return to the xanthate procedure as the best method for the preparation of the cyclobutene 100. Hydrogenation of 100 followed by deprotection of the aldehyde would yield the cis

isomer of the key intermediate **64** as illustrated in Scheme 1-20.

Careful sequential treatment of the alcohol **97** with potassium hydride, carbon disulfide, and methyl iodide yielded the cyclobutene **100** and a small amount of the xanthate **99**. These products were separated by preparative thick layer chromatography. The ^{1}H NMR spectrum of cyclobutene **100** exhibited the anticipated signals with consistent chemical shifts and coupling patterns. Thus two singlets at 0.78 and 1.28 ppm each of which integrated to three protons were assigned to the methyl groups at position 5 of the dioxane ring. A doublet of doublets at 2.56 ppm, J = 12 and 2 Hz, and a doublet of doublets at 3.30 ppm, J = 12 and 4 Hz, which integrated to 1 proton each were assigned to the prochiral methylene protons of the cyclobutene ring. A doublet at 3.62 ppm, J = 12 Hz, and a doublet at 3.77 ppm, J = 12 Hz, which integrated to 2 protons each were assigned to the methylene protons at positions 4 and 6 of the dioxane ring. Singlets at 3.73 and 3.80 ppm which integrated to 3 protons each were assigned to the methoxy groups of the dimethoxyphenyl ring. A multiplet at 4.25 ppm which integrated to 1 proton was assigned to the benzylic methine of the cyclobutene ring. A singlet at 5.37 ppm which integrated to 1 proton was assigned to the benzylic methine of the dioxane ring. A doublet at 6.53 ppm, J = 2 Hz, which integrated to 1 proton was assigned to the olefinic proton of the cyclobutene ring. A doublet of doublets at 6.69 ppm, J = 10 and 3 Hz, a doublet at 6.77 ppm,

Scheme 1-20: Synthetic route to compound **64**


CHO
H
H
MeO
OMe
64
TsOH
O
106
O
O
H
H
MeO
OMe
>99%
<1%
CHO
H
H
MeO
OMe
65
TsOH
O
107
O
O
H
H
MeO
OMe
H2
Pd/C
100
OMe
OMe
1) KH
2) CS2
3) MeI
97
OH
OMe
OMe

J = 10 Hz, and a doublet at 6.84 ppm, J = 3 Hz, each of which integrated to 1 proton were assigned to the protons of the dimethoxyphenyl ring. Doublets at 7.38 ppm, J = 8 Hz, and 7.46 ppm, J = 8 Hz, each of which integrated to 2 protons were assigned to the protons of the aromatic ring bonded to the dioxane ring. The ^{13}C NMR spectrum of the product was consistent with compound **100**. Comparing the observed chemical shifts with predicted values, the DEPT ^{13}C NMR spectrum and the ^{1}H-^{13}C heteronuclear correlation spectrum the following peak assignments were made: the methyl carbons at position 5 of the dioxane ring were assigned to two signals at 21.7 and 22.8 ppm. The quaternary carbon at position 5 of the dioxane ring was assigned the signal at 30.0 ppm. The signal at 37.0 ppm was assigned to the benzylic, allylic methine carbon of the cyclobutene ring. The methylene carbon of the cyclobutene ring was assigned to the signal at 37.4 ppm. The methyl carbons of the two methoxy groups were assigned to signals at 55.5 and 55.9 ppm. The methylene carbons at positions 4 and 6 of the dioxane ring were assigned to the signal at 77.4 ppm. The benzylic methine carbon of the dioxane ring was assigned to the signal at 101.3 ppm. Signals at 110.8, 111.1, and 113.5 ppm were assigned to the dimethoxy phenyl ring carbons bearing the protons. The carbons bearing protons of the aromatic ring bonded to the dioxane ring were assigned to signals at 124.3 and 125.9 ppm. The signal at 128.5 ppm was assigned to the olefinic carbon bearing the proton. The

olefinic carbon bonded to the aromatic ring was assigned to the signal at 133.2 ppm. The dimethoxy phenyl ring carbon bonded to the cyclobutene ring was assigned to the signal at 134.9 ppm. Two signals at 137.7 and 145.9 ppm were assigned to the aromatic ring carbons bonded to the double bond of the cyclobutene and to the dioxane ring. The dimethoxyphenyl ring carbons bonded to the methoxy groups were assigned to the signals at 151.4 and 153.4 ppm. The mass spectrum of the product (parent ion at m/e = 380 and the absence of a strong m/e = 164 signal) is consistent with compound 100. The retro 2+2 ring opening reaction which gave a strong m/e = 164 signal in the mass spectrum of the other 4 membered ring species analyzed did not occur in compound 100. This is consistent with this 4 membered ring being unsaturated.

The ^{1}H NMR spectrum of the xanthate 99 showed signals with chemical shifts and coupling patterns consistent with that expected for structure 99. Thus two singlets at 0.79 and 1.29 ppm which integrated to 3 protons each were assigned to the methyl groups at position 5 of the dioxane ring. A singlet at 2.25 ppm which integrated to 3 protons was assigned to the S-methyl of the xanthate. Multiplets at 2.86 ppm and at 3.23 ppm which integrated to 2 protons each were assigned to the prochiral methylene protons of the cyclobutane ring. A multiplet at 3.58 ppm which integrated to 1 proton was assigned to the benzylic methine of the cyclobutane ring. Singlets at 3.67 and 3.78 ppm which integrated to 3 protons

each were assigned to the methoxy groups of the dimethoxyphenyl ring. A doublet at 3.71 ppm, J = 11 Hz, and a doublet at 3.79 ppm, J = 11 Hz, which integrated to 2 protons each were assigned to the methylene protons at positions 4 and 6 of the dioxane ring. A singlet at 5.40 ppm which integrated to 1 proton was assigned to the benzylic methine of the dioxane ring. A multiplet at 6.68 ppm which integrated to 2 protons and a doublet at 6.85 ppm, J = 2 Hz, which integrated to 1 proton were assigned to the protons of the dimethoxyphenyl ring. Doublets at 7.51 ppm, J = 8 Hz, and 7.65 ppm, J = 8 Hz, each of which integrated to 2 protons were assigned to the protons of the aromatic ring bonded to the dioxane ring. The ^{13}C NMR spectrum of the product was consistent with compound 99. Comparing the observed chemical shifts with predicted values, the DEPT ^{13}C NMR spectrum and the ^{1}H-^{13}C heteronuclear correlation spectrum the following peak assignments were made: the S-methyl carbon of the xanthate group was assigned to the signal at 12.7 ppm. The methyl carbons at position 5 of the dioxane ring were assigned to two signals at 21.9 and 23.1 ppm. The quaternary carbon at position 5 of the dioxane ring was assigned the signal at 30.3 ppm. The signal at 31.5 ppm was assigned to the benzylic methine carbon of the cyclobutane ring. The methylene carbons of the cyclobutane ring were assigned to the signal at 42.6 ppm. The signal at 51.5 ppm was assigned to the quaternary carbon of the cyclobutane ring. The methyl carbons

of the two methoxy groups were assigned to signals at 55.77 and 55.80 ppm. The methylene carbons at positions 4 and 6 of the dioxane ring were assigned to the signal at 77.7 ppm. The benzylic methine carbon of the dioxane ring was assigned to the signal at 101.6 ppm. Signals at 111.0, 111.1, and 113.6 ppm were assigned to the dimethoxy phenyl ring carbons bearing the protons. The carbons bearing protons of the aromatic ring bonded to the dioxane ring were assigned to signals at 126.0 and 127.5 ppm. The dimethoxy phenyl ring carbon bonded to the cyclobutane ring was assigned to the signal at 133.0 ppm. Two signals at 137.1 and 144.9 ppm were assigned to the carbons which are bonded to the cyclobutane and to the dioxane ring, of the aromatic ring linking the cyclobutane and dioxane rings. The dimethoxyphenyl ring carbons bonded to the methoxy groups were assigned to the signals at 151.5 and 153.0 ppm. The signal at 188.1 ppm was assigned to the carbon of the thiocarbonyl group. The mass spectrum of the product (parent ion at m/e = 488 and major fragment at m/e = 164 corresponding to a retro 2+2 ring cleavage) is consistent with compound 99.

The isolated yield of xanthate 99 was so low that its use to make both species 106 and 107 by radical reduction was impractical. An attempt was, however, made and the xanthate was treated with 2,2'-azobisisobutyronitrile and tributyl tin hydride to give a mixture of two major and several minor products, as detected by TLC. One of the major products was

the same, as determined by TLC analysis, as the product obtained from the hydrogenation of cyclobutene **100**. The separation of these products was so difficult and the yield so low that no further characterization data could be obtained.

In order to convert the cyclobutene **100** to **106** it was decided to use as mild a hydrogenation catalyst as possible in hope that the use of a mild catalyst would minimize the possibility of hydrogenolysis of the acetal function (50). The catalyst selected was 0.5% Rh on Al_2O_3. A trial scale hydrogenation with this catalyst was successful, although the reaction proceeded very slowly. During a series of trial reactions on styrene, to determine optimum conditions, it was noted that the reactions proceeded even more slowly as time passed. This suggested that the catalyst was being poisoned. Storing the catalyst in a vacuum oven for 7 days partially restored its activity, although this was short lived. Due to these problems a different catalyst was sought.

The possible suitability of PtO_2, selected because of availability, was tested using a mixture of styrene and 2-(4-bromophenyl)-4,4-dimethyl-1,3-dioxane **92**. The latter was included in order to test the stability of the acetal function to these conditions. GLC analysis of the reaction mixture indicated complete clean conversion of the alkene to the alkane while **92** was untouched. This catalyst was then successfully tested on the cyclobutene **100**.

Hydrogenation of cyclobutene **100** yielded one product, presumably species **106**, the *cis* isomer. The ^{1}H NMR spectrum of the product showed the loss of the olefinic signal of **100**. The signals corresponding to the protons of the cyclobutane ring were observed as two multiplets at 2.16 and 2.74 ppm which integrated to 2 protons each, and a multiplet at 3.47 ppm which integrated to 1 proton. These signals were assigned to the prochiral methylene protons and one of the two benzylic methine protons respectively. Integration of the spectrum suggested that the second benzylic methine proton was buried under signals arising from the methoxy and acetal groups. The observed chemical shifts of these signals are consistent with the formation of species **106**, or of the *trans* isomer **107**. The stereoselective nature of this hydrogenation reaction was consistent with the observation of only one signal for the benzylic methine proton of the dioxane ring. The coupling pattern within the cyclobutane ring protons was not readily interpretable even with the aid of ^{1}H-^{1}H decoupling. It was therefore not possible to determine by direct observation which isomer was formed. The assumed *cis* stereochemistry of the product will however be further justified below. The ^{13}C NMR spectrum of the product was also consistent with a stereoselective reduction of the double bond. The signals assigned to the olefinic carbons of **100** were absent. The benzylic methine carbons of the cyclobutane ring were observed as only two signals, at 31.4 and 36.4 ppm.

The methylene carbons of the cyclobutane ring were observed as a single signal at 36.3 ppm. The mass spectrum of the product (parent ion at m/e = 382 and the reappearance of a strong fragment at m/e = 164 corresponding to a retro 2+2 ring opening of the cyclobutane ring) is consistent with species **106**.

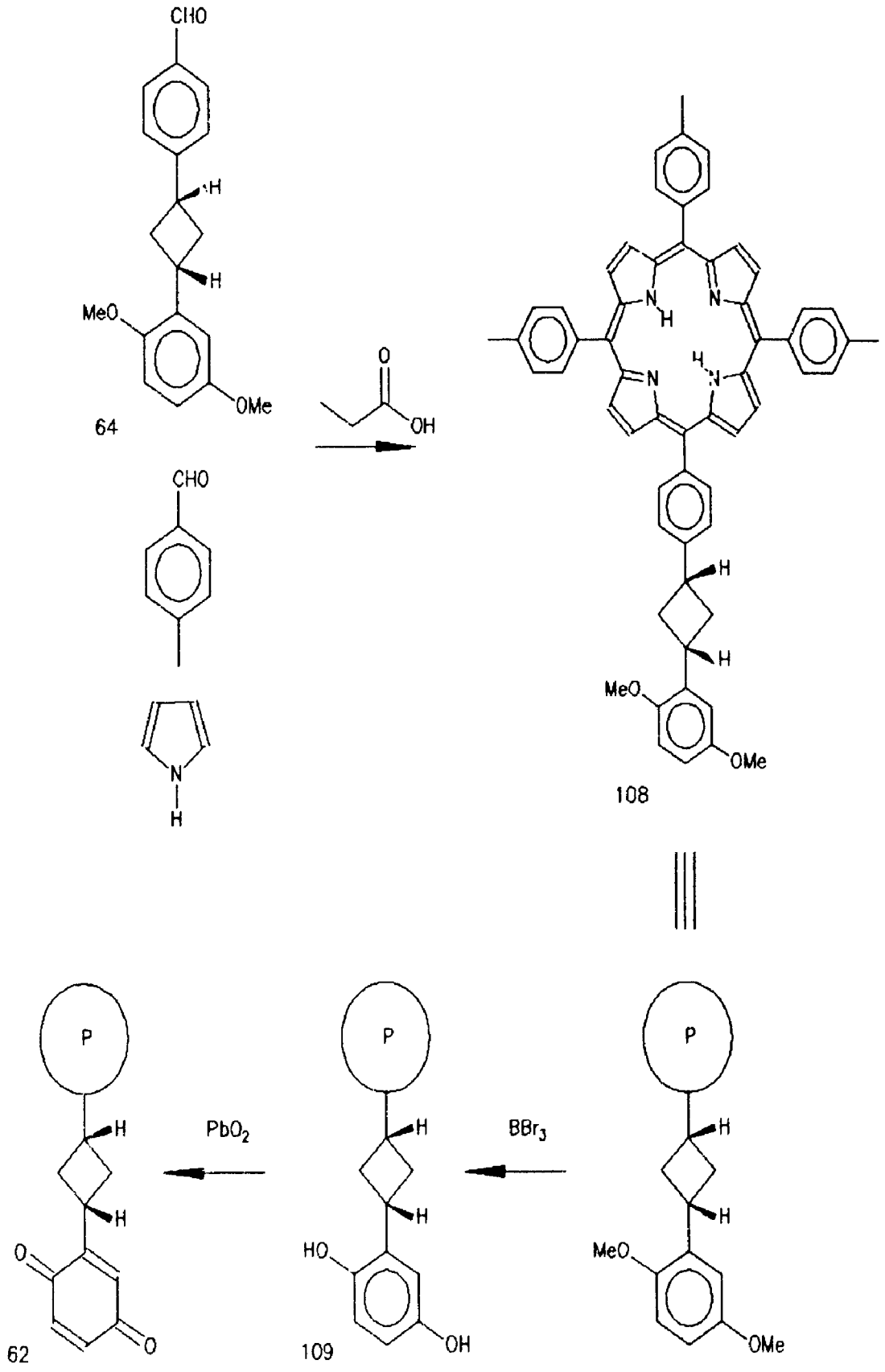
The acetal protecting group of species **106** was easily removed by refluxing with a catalytic amount of p-toluenesulfonic acid in acetone. Under these conditions acetone presumably acted as both solvent and as a sacrificial carbonyl; the major by-product of this reaction although neither detected nor isolated was presumed to be 2,2,5,5-tetramethyl-1,3-dioxane. These conditions were not expected to have any effect on the stereochemistry about the cyclobutane ring. Therefore, the presumed *cis* starting material **106** was assumed to yield the *cis* product, species **64**. The ^{1}H NMR spectrum of the product showed signals with chemical shifts and coupling patterns consistent with the formation of the *cis* product **64**. Thus, a doublet of triplet of triplets at 2.22 ppm, J = 11, 11, and 2.5 Hz respectively, which integrated to 2 protons and a doublet of triplet of quartets at 2.81 ppm, J = 8, 7.5, and 2.5 Hz respectively, which also integrated to 2 protons were assigned to the prochiral methylene protons of the cyclobutane ring. A triplet of triplets at 3.56 ppm, J = 9 and 7.5 Hz, and a triplet of triplets at 3.69 ppm, J = 9 and 7.5 Hz, which

integrated to 1 proton each were assigned to the two benzylic methine protons of the cyclobutane ring. As will be argued below, this coupling pattern is consistent with cis stereochemistry about the cyclobutane ring. Two singlets at 3.76 and 3.77 ppm which integrated to 3 protons each were assigned to the two methoxy groups. The aromatic ring protons of the dimethoxyphenyl ring appeared as a doublet of doublets at 6.67 ppm, J = 8 and 3 Hz, a doublet at 6.76 ppm, J = 8 Hz, and a doublet at 6.77 ppm, J = 3 Hz, which integrated to 1 proton each. The aromatic ring protons of the aldehyde substituted phenyl ring appeared as a doublet at 7.37 ppm, J = 8 Hz, and a doublet at 7.80 ppm, J = 8 Hz, which integrated to 2 protons each. Finally, and most importantly, the aldehyde proton was seen as a one proton singlet at 9.95 ppm. The appearance of a single signal for the aldehyde proton is consistent with the product being a single isomer. The ^{13}C NMR spectrum of the product was also consistent with structure 64 and with the product being a single isomer. Signals at 31.5 and 36.6 ppm were assigned to the benzylic methine carbons of the cyclobutane ring. The methylene carbons of the cyclobutane ring were assigned to the signal at 36.0 ppm. The carbons of the methoxy groups were assigned to signals at 55.7 and 55.9 ppm. Signals at 110.5, 111.1 and 114.0 ppm were assigned to the carbons bearing protons of the dimethoxyphenyl ring. The carbons bearing protons of the benzaldehyde ring were assigned to signals at 127.2 and 129.9 ppm. The aromatic ring carbons bonded to the

cyclobutane ring were assigned to signals at 134.3 and 134.5 ppm. Signals at 151.8, 153.0 and 153.6 ppm were assigned to the aromatic ring carbons bonded to the methoxy and aldehyde functions. The aldehyde carbon appeared as a single peak at 192.0 ppm. Infra-red analysis of the product revealed the carbonyl stretch at 1697 cm^{-1} consistent with values expected for aromatic aldehydes. The mass spectrum of the product (parent ion at m/e = 296 and major fragment at m/e = 164 corresponding to a retro 2+2 ring opening) is consistent with compound 64.

The synthetic route from the key intermediate 64 to the final cyclobutane linked porphyrin benzoquinone 62 is outlined in Scheme 1-21. Following the general procedure of Anton and Loach (33) for the preparation of substituted tetra-phenyl porphyrins, the aldehyde 64 was combined with excess (ca. 1:100) p-tolualdehyde and pyrrole in refluxing propionic acid. The large excess of tolualdehyde was used to minimize the formation of porphyrin products which incorporated more than one molecule of 64. The crude product obtained from this reaction was anticipated to be a mixture of tetratolyl porphyrin (TTP) and the desired dimethoxyphenyl porphyrin (P4DMB) 108, in approximately a 25:1 ratio. This product ratio is based on the reasonable assumption that the aldehydes are incorporated into the porphyrin products in a statistical manner. Following removal of most of the TTP by column chromatography, the product rich fraction was purified by preparative thick layer chromatography on non-fluorescent

Scheme 1-21: Synthetic route to compound **62**


CHO
MeO
OMe
64
O
OH
CHO
N
H
H
H
H
N
H
N
N
H
MeO
OMe
108
P
H
H
MeO
OMe
BBr3
P
H
H
HO
OH
109
PbO2
P
H
H
O
O
62

silica gel, to yield 108 (P4DMB) in an 11.6% yield, based on total starting aldehyde 64. Non-fluorescent silica gel was used for purification to avoid metalating the product (the fluorophor used in commercial UV active silica gel contains zinc which can be sequestered by porphyrins). Metalation of the porphyrin would change its symmetry from D_2h to D_4h and thereby significantly alter its optical properties. The isolated yield of 11.6% is excellent considering the number of carbon bonds which were formed during the reaction. The ^1H NMR spectrum of this product showed a broad singlet at -2.75 ppm (ie upfield from TMS) which integrated to 2 protons attributed to the N-H protons in the center of the porphyrin ring. These protons are normally found at this high a field due to the ring current associated with the porphyrin ring. The methylene protons of the cyclobutane ring were observed as a doublet of triplet of triplets, J = 11, 11 and 2.5 Hz, at 2.53 ppm and a doublet of triplet of quartets, J = 15, 8 and 2.5 Hz, at 3.03 ppm which integrated to 2 protons each. Integration of the spectrum indicated that the benzylic methine protons of the cyclobutane ring, which were not clearly observable, were partially buried under signals arising from the methoxy groups. A singlet at 2.70 ppm which integrated to 9 protons was assigned to the tolyl methyl protons. Only two of these methyl groups are in identical environments but all three are apparently coincidentally at the same chemical shift. The methoxy groups were observed as two three proton singlets at 3.83 and 3.86 ppm. The aromatic

ring protons of the dimethoxyphenyl ring were observed as a doublet of doublets at 6.73 ppm, J = 8 and 3 Hz, a doublet at 6.82 ppm, J = 8 Hz, and a doublet at 6.99 ppm, J = 3 Hz, which integrated to 1 proton each. The 12 protons of the three tolyl aromatic rings appeared as AA' BB' coincident pairs of doublets, J = 8 Hz, at 7.54 and 8.10 ppm. This pattern is characteristic of tetra aryl porphyrins due to the fact that the protons on the aryl groups are drawn downfield by the porphyrin ring which acts as an electron withdrawing substituent. The same pattern was also seen for the phenyl ring between the porphyrin and cyclobutane rings which exhibited a pair of doublets at 7.62 and 8.14 ppm, J = 8 Hz, each integrating to 2 protons. The protons at the 2,3,7,8,12, 13,17 and 18 positions of the porphyrin ring (ie those on the β-positions of the pyrrole rings) appeared as a broadened singlet at 8.87 ppm which integrated to 8 protons. These protons appear uncoupled at 200 MHz as their environments are so similar.

The ^{13}C NMR spectrum of the product was consistent with compound 108. Comparing the observed chemical shifts with predicted values, the DEPT ^{13}C NMR spectrum and the ^{1}H-^{13}C heteronuclear correlation spectrum the following peak assignments were made: the signal at 21.6 ppm was assigned to the three tolyl methyl carbons. Although one of these methyl carbons is in a slightly different environment than the other two all three are observed coincidently at the same shift. The benzylic methine carbons of the cyclobutane ring were

observed as a single peak at 31.6 ppm. These carbons are in different environments however they are observed to be coincident. The methylene carbons of the cyclobutane ring are assigned the peak at 36.7 ppm. Peaks at 55.8 and 56.1 ppm were assigned to the carbons of the methoxy groups. The carbons bearing the protons of the dimethoxyphenyl ring were assigned to the peaks at 110.5, 111.2 and 114.2 ppm. Signals at 120.1 and 120.2 ppm were assigned to carbons at position 5 and positions 10, 15 and 20 of the porphyrin ring. Although the carbon at position 15 is in a slightly different environment than those at positions 10 and 20 they are observed as a single signal. The signal at 124.9 ppm was assigned to the carbon atoms at positions 2, 3, 7, 8, 12, 13, 17 and 18 of the porphyrin ring (the β-positions of the pyrrole rings). Although these carbons may be divided into four pairs each with a slightly different environment they are observed to be coincident. The aromatic ring carbons bearing the protons of both the tolyl groups and the phenyl group linking the porphyrin and the cyclobutane rings were observed as two signals at 127.4 and 134.6 ppm. Again these carbons are coincidentally at the same shifts. The very broad signal observed at ca. 130 ppm was assigned to the carbon atoms at positions 1, 4, 6, 9, 11, 14, 16 and 19 of the porphyrin ring (the α-positions of the pyrrole rings). The signal at 134.9 ppm was assigned to the carbon of the dimethoxyphenyl ring bonded to the cyclobutane ring. The tolyl ring carbons bonded to the methyl groups were assigned to the signal at

137.3 ppm. The tolyl ring carbons bonded to the porphyrin ring were assigned to the signal at 139.4 ppm. The signal at 139.8 ppm was assigned to the carbon of the aromatic ring linking the porphyrin and cyclobutane rings bonded to the porphyrin ring. The carbon of this phenyl ring bonded to the cyclobutane ring was assigned to the signal at 145.0 ppm. Finally the carbons of the dimethoxyphenyl ring bonded to the methoxy groups were assigned to signals at 151.9 and 153.7 ppm.

The mass spectrum of the product (parent ion at m/e = 846 and major fragment at m/e = 682) is consistent with P4DMB compound **108**. As has been pointed out for earlier compounds in the synthetic pathway a major fragmentation pathway for compounds containing the cyclobutane moiety has been a retro 2+2 cyclization. This is evidenced by the major fragment m/e = 164, which is attributable to the radical cation of 2,5-dimethoxystyrene, present in the fragmentation pattern of these species. The fragmentation pattern of P4DMB **108** also proceeds via a similar retro 2+2 cyclization. In this case however the m/e = 164 ion is not detected as a major fragment, rather the major fragment detected is attributable to loss of 2,5-dimethoxystyrene from the parent ion, *ie* m/e = 682 (846 - 164).

The UV/vis spectrum of the product in methylene chloride revealed a strong band at 418 nm. The position of this porphyrin band, referred to as the Soret band, is a function of the symmetry of the porphyrin ring. Free base porphyrins,

even those unsymmetrically substituted with remote substituents, behave as though they possess D_2h symmetry. These porphyrins exhibit the Soret absorbance at ca. 420 nm, and the exact location of the band is a function of solvent. Porphyrins which have been metalated or twice protonated in the center of the porphyrin ring behave as though they possess D_4h symmetry. These porphyrins exhibit the Soret absorbance at ca. 440 nm. In addition to this characteristic shift in the location of the Soret band there are also changes in the number of Q-bands associated with the change in symmetry. D_2h porphyrins exhibit 4 absorption bands in the 500 - 650 nm range, which are collectively referred to as the Q-bands. D_4h porphyrins exhibit only two Q-bands. The observed location of the Soret band and the fact that 4 Q-bands were observed indicates that the product was isolated as the free base porphyrin.

A sample of P4DMB was set aside for absorbance and fluorescence measurements. It was intended that half the remaining material be deprotected with boron tribromide to give the porphyrin hydroquinone species ($P4QH_2$) 109. The $P4QH_2$ sample was to be used for characterization, absorbance and fluorescence measurements. It was also intended that portions of this material be oxidized with lead dioxide to the porphyrin quinone species (P4Q) 62 for absorbance and fluorescence measurements. After the photophysics of this system had been established, the balance of $P4QH_2$ was to be oxidized to P4Q, for purposes of characterization. Before

proceeding with deprotection of the dimethoxy compound **108** (P4DMB), it was decided to attempt the reaction on a model. Thus treatment of m-methoxyacetophenone with boron tribromide resulted in the clean formation of m-hydroxyacetophenone, as detected by TLC.

The methyl ether groups of P4DMB **108** were successfully cleaved by treatment with boron tribromide in methylene chloride at -78°C to give P4QH$_2$ **109**. The product was purified by preparative thick layer chromatography in subdued light. Subdued light was necessary to avoid possible photo-oxidation of the hydroquinone ring. The ^{1}H NMR spectrum of the product showed a broad singlet at -2.80 ppm which integrated to 2 protons indicating that the N-H protons in the middle of the porphyrin ring were still present. The 1,3-diaryl substituted cyclobutane ring was also still present as indicated by a 2 proton doublet of triplet of triplets, J = 8, 8 and 2.5 Hz, at 2.54 ppm and a 2 proton doublet of triplet of quartets, J = 11, 11 and 2.5 Hz, at 3.04 ppm assigned to the methylene protons and a 2 proton multiplet at 3.80 ppm corresponding to the methine protons. A singlet at 2.69 ppm which integrated to 9 protons was assigned to the tolyl methyl protons. The new hydroquinone OH protons appeared as a broad singlet at 4.44 ppm, while the aromatic protons of the hydroquinone were seen in approximately the same position and with the same coupling pattern as in **108**. Thus, a doublet of doublets at 6.58 ppm, J = 8 and 3 Hz, a doublet at 6.67 ppm, J = 8 Hz, and a doublet at 6.83 ppm, J = 3 Hz, were observed with each

integrating to 1 proton. Similarly the aromatic protons of the porphyrin ring were largely unchanged.

The ^{13}C NMR spectrum of the product was consistent with compound 109. The cyclobutane ring carbons were observed as three signals: 31.2 and 36.6 ppm for the two methine carbons and 36.3 ppm for the methylene carbons. The signals assigned to the aromatic carbons bearing the protons of the hydroquinone ring were observed approximately 3 ppm downfield from their shifts in 108, ie 113.4, 114.4 and 116.0 ppm. The signals assigned to the carbon bonded to the cyclobutane ring, 132.3 ppm, and to the carbons bonded to the OH groups, 147.5 and 149.6 ppm, were shifted upfield ca. 4 ppm relative to their shifts in 108. These changes, with the exception of the direction of the change for the carbon bonded to the cyclobutane ring, are in agreement with those expected based on the conversion of 108 to the hydroquinone 109. The 56 ppm signals observed in the spectrum of 108 and assigned to the methoxy carbons are absent in the spectrum of 109. The signals attributable to the balance of 109 were observed to be not significantly altered from their chemical shifts in 108.

The mass spectrum of the product (parent ion at m/e = 818 and major fragment at m/e = 682 corresponding to the loss of dihydroxystyrene from a retro 2+2 cyclization reaction) is consistent with compound 109. The observation of a strong absorption band for the product at 418 nm in methylene chloride solution indicated the product had been isolated as

the free base porphyrin. The absence of noticeable changes in the UV-vis spectrum of 109 relative to that of 108, and indeed relative to that of TTP, indicated that there was no appreciable interaction between the hydroquinone ring and the porphyrin chromophore.

The oxidation of $P4QH_2$ 109 to P4Q 62 for characterization purposes was achieved by shaking a methylene chloride solution of $P4QH_2$ with lead dioxide powder for 20 minutes (5). The reaction mixture was filtered and evaporated to dryness. ^1H NMR analysis of the residue indicated the presence of trace impurities. These were removed by preparative thick layer chromatography. The ^1H NMR spectrum of the purified product was consistent with oxidation of 109 to yield 62. The protons of the cyclobutane ring were, for the first time, observed as four well resolved multiplets. The observed separation of the methine signals is due to the proximity of the quinone ring, resulting in significantly different environments for the two methine protons. The signals due to the protons of the quinone ring are also significantly altered relative to the hydroquinone species 109. These signals appear as broad unresolved "singlets" void of the 8 and 3 Hz coupling observed in the precursor species. These changes and the absence of the hydroquinone OH proton signal are the only observed differences between the ^1H NMR spectra of 109 and of 62. The coupling pattern observed within the cyclobutane ring protons will be discussed below.

The ^{13}C NMR spectrum of the product showed large changes in the chemical shifts of the quinone ring carbons relative to the those of the hydroquinone while the balance of the spectrum was largely unchanged from that of **109**. The aromatic carbons bearing the protons of the quinone ring were shifted downfield ca. 20 ppm relative to the hydroquinone ring as a result of the oxidation. Thus, these carbons were observed at 131.0, 136.4 and 137.0 ppm. The quinone ring carbon bonded to the cyclobutane ring, observed at 151.7 ppm, was also shifted downfield ca. 20 ppm relative to the hydroquinone ring. The carbonyl carbons of the quinone ring were observed at 187.6 and 188.0 ppm, ca. 40 ppm downfield relative to the hydroquinone ring. These large changes are consistent with the oxidation of the hydroquinone to the quinone.

Mass spectral analysis of P4Q proved problematical. Although the parent ion of m/e = 816 could be detected, it was not stable. Within the first 30 seconds after the sample probe was placed in the ionization chamber of the mass spectrometer, the electron beam apparently reduced P4Q to $P4QH_2$ and a new molecular ion was seen at m/e = 818. The identity of $P4QH_2$ was confirmed by both exact mass and by comparison of the observed fragmentation pattern with that from authentic $P4QH_2$. Rapid reduction of the quinone prevented even brief detection of the 816 parent ion if chemical ionization was used. Although unfortunate, this does

indicate that the lead dioxide oxidation of the hydroquinone ring had no effect on other portions of the molecule.

The UV-vis spectrum of the product revealed the classic D_2h porphyrin pattern. The Soret band was observed at 418 nm in methylene chloride solution. The longer wavelength Q-band region of the spectrum showed four absorption bands as expected for a free base porphyrin. This proves that no stable complex was formed between the porphyrin ring and a lead atom from the oxidizer.

The hydrogenation of cyclobutene **100** to give cyclobutane **106** was assumed to proceed via *cis* addition of H_2 from the least hindered face so that the aryl groups on the cyclobutane ring in **106**, **64**, **108**, and **109** were assumed to be *cis*. In all of these compounds the stereochemistry of the substituents could not be confirmed by ^{1}H NMR since the cyclobutane protons were either masked by other signals or superimposed on each other. However, in **62** the cyclobutane protons were all distinct and the splitting pattern and coupling constants could be determined. Thus it was possible to confirm the assumed *cis* stereochemistry of the cyclobutane ring in **62** by ^{1}H NMR decoupling. The signals of interest were the one proton multiplets at 3.91 (H_a) and 3.64 (H_b) ppm (corresponding to the cyclobutane methines) and the pair of two proton multiplets at 2.96 (H_c) and 2.40 (H_d) ppm (corresponding to the cyclobutane methylenes, one signal for the protons *cis* to the quinone ring and one for the protons *trans* to it). The methine signals at 3.64 and 3.91 ppm were

each a triplet of triplets, J values 7 and 9 Hz. The methylene signals at 2.40 and 2.96 ppm appeared as doublets of triplets which were confused by the presence of small J value couplings. The 2.96 ppm signal appeared to be a doublet, J ca. 11 Hz, of triplets, J ca. 7 Hz. The 2.40 ppm signal appeared to be a doublet, J ca. 11 Hz, of triplets, J ca. 9 Hz.

Saturation of H_d, the 2.40 ppm methylene multiplet, resulted in the H_c signal collapsing to a crude triplet, J = 7 Hz. The H_b and H_a methine signals also collapsed to triplets, each with J = 7 Hz. Similarly, saturation of H_c resulted in the H_d signal collapsing to a crude triplet, J = 9 Hz, and the H_b and H_a methine signals collapsing to triplets, each with J = 9 Hz. The appearance of each methine multiplet was not affected by saturation of the other methine signal, indicating the methine protons were not coupled strongly to each other. The appearance of the methylene signals upon saturation of either of the methine signals was not simply a pair of doublet of doublets; rather each methylene multiplet collapsed to a pattern resembling a doublet of doublets but confused by the presence of small J value couplings. J values within these patterns could not be determined accurately. The coupling patterns displayed by the methylene multiplets were different from each other but were constant regardless of which methine signal was saturated. In other words the coupling pattern displayed by H_d upon saturation of H_b was superimposable on that obtained from

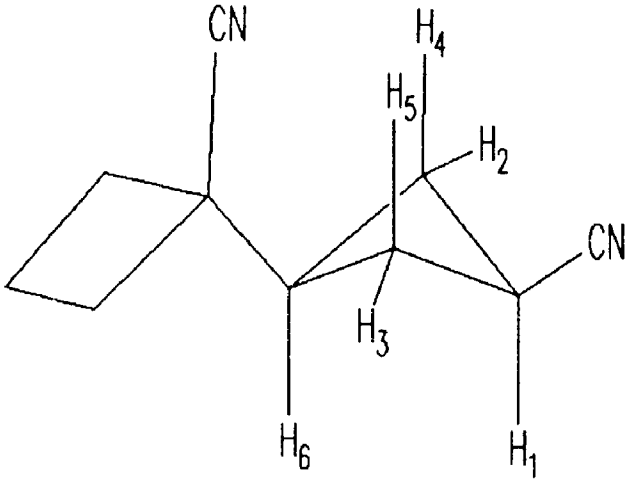
saturating H_a. Similarly, the coupling pattern displayed by H_c upon saturation of H_b was superimposable on that obtained from saturating H_a. This behavior indicates that $J_{ac} = J_{bc}$ and $J_{ad} = J_{bd}$. This is only possible if the relative time averaged orientation of H_a with respect to H_c and H_d is identical to that of H_b. This can only be true if H_a and H_b are cis, and therefore the aryl substituents on the cyclobutyl ring must also be cis.

The cis stereochemical assignment in 62 was supported by the reported coupling constants for species 110 and 111 (51), as illustrated in Figure 1-17. The methine proton H_1 of the cis isomer 110 is coupled to the methylene protons with coupling constants of 8.4 and 9.8 Hz. The methine proton H_1 of the trans isomer 111 is coupled to the methylene protons with coupling constants of 4.6 and 9.6 Hz. The observed coupling constants between the methine protons and the methylene protons of P4Q were ca. 7 and ca. 9 Hz. These values and the difference between the two values are closer to those reported for the cis isomer 110.

ii - Measurement of Electron Transfer Rate Constants

With P4Q (compound 62) in hand and with its structure secure its photoinduced intramolecular electron transfer properties could be investigated. Before beginning this discussion, however, a brief overview of the relevant background theory will be given.

Figure 1-17: ^{1}H - ^{1}H J values in the cis and trans 1,3-disubstituted cyclobutane species **110** and **111**

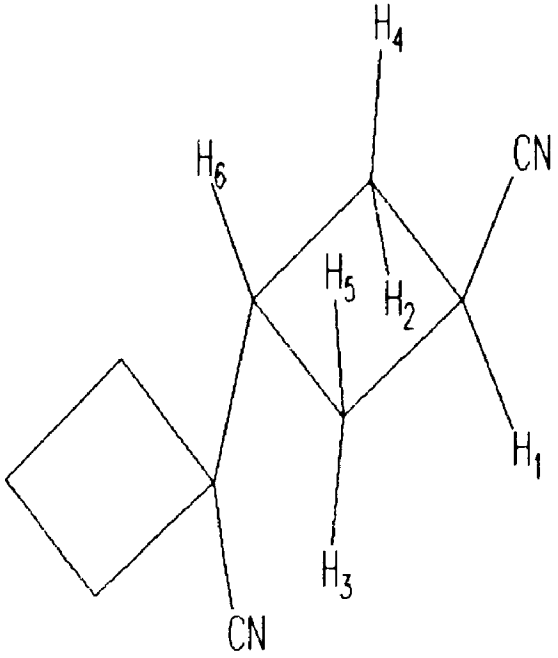


$J_{12} = J_{13} = 8{\cdot}39$ Hz

$J_{14} = J_{15} = 9{\cdot}79$ Hz

$J_{16} < 0{\cdot}3$ Hz

110



$J_{12} = J_{13} = 4{\cdot}59$ Hz

$J_{14} = J_{15} = 9{\cdot}57$ Hz

$J_{16} = -1{\cdot}23$ Hz

111

In the absence of photochemical reaction or photochemical electron transfer, an isolated molecule in its lowest excited singlet state S_1 will meet one of three fates, as illustrated in Figure 1-18. It may decay radiatively (fluorescence) to the ground state S_0 with a rate constant k_f, it may decay non-radiatively (internal conversion) to the ground state with a rate constant k_{ic}, or it may intersystem cross to the triplet manifold with a rate constant k_{isc}.

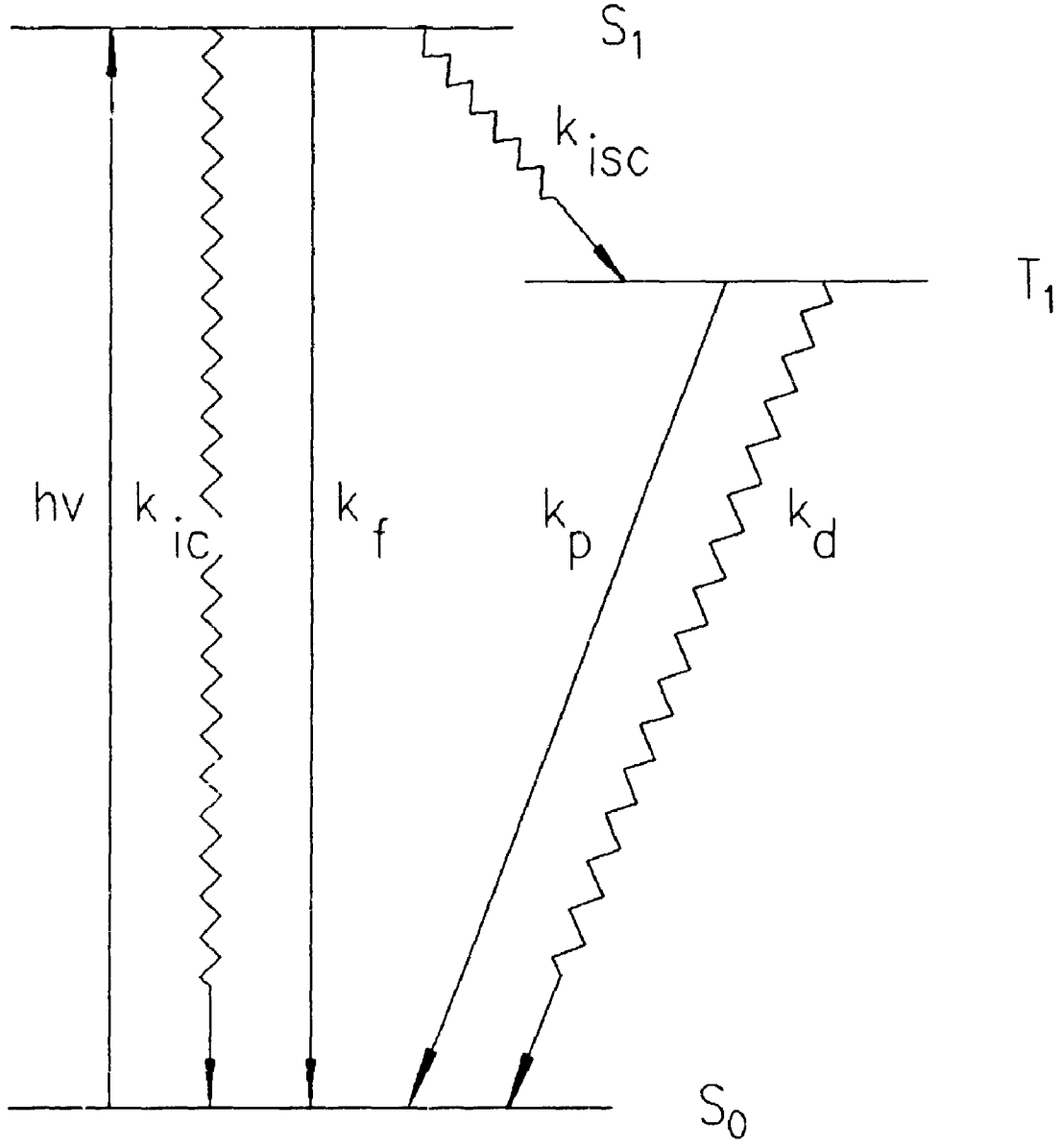
The lifetime of the excited singlet state, τ, is defined in terms of these unimolecular rate constants by equation 1-2.

$$\tau = (k_f + k_{ic} + k_{isc})^{-1} \qquad - (1\text{-}2)$$

Time resolved fluorescence emission spectroscopy can be used to obtain the value of τ. This can be done using the technique of time correlated single photon counting (52).

This technique is based on the assumption that the probability of the excited state emitting a photon, and of that photon being detected, at any given time after excitation follows a distribution curve which is identical to the total emission intensity vs. time curve. By measuring the time elapsed between excitation and emission of a large number of photons (5×10^3 counts in the peak channel were typically collected in this study) a distribution curve can be constructed which represents the decay profile of the excited state. The decay profile so collected must be corrected for the fact that excitation of the sample was not instantaneous,

Figure 1-18: Jablonski diagram for an isolated molecule

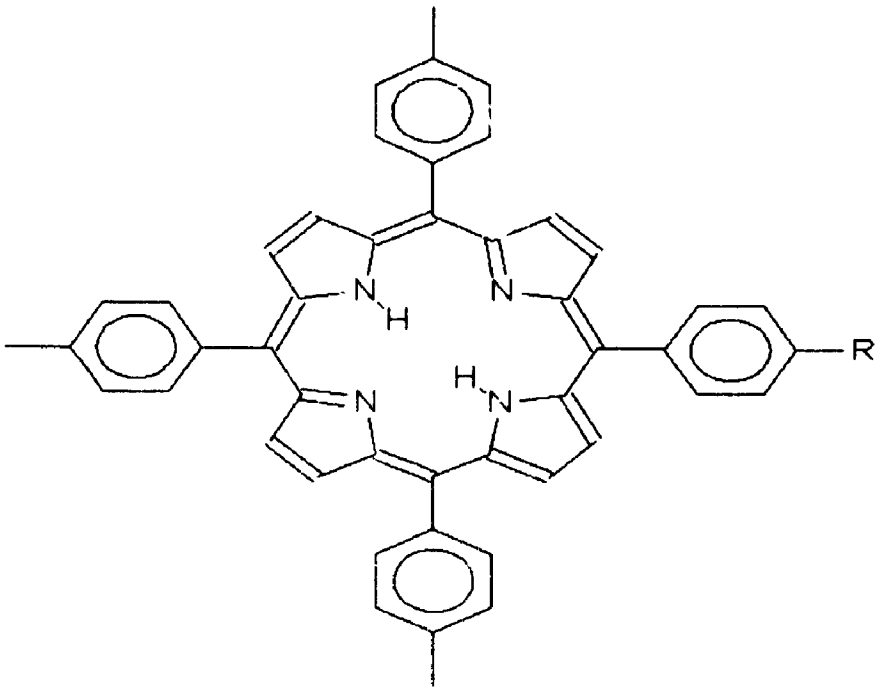

S1
k isc
T1
hv
k ic
k f
k p
k d
S0

but rather that it occurred non-uniformly within a finite time envelope. This correction takes the form of a deconvolution of the excitation source profile from the observed decay profile. The excitation source profile is measured using a colloidal suspension of silica in water as a light scattering agent.

Tetratolyl porphyrin (TTP, **112**) was used as an example of an isolated porphyrin. The fluorescence lifetime of TTP was determined in six solvents, and the values are given in Table 1-2. Single exponential decays were seen in all cases, indicating that in all the solvents the TTP was decaying from a single excited state by a combination of first order processes. The shortening of the lifetimes in the halogenated solvents was attributed to increased intersystem crossing in these solvents. This was rationalized as a solvent heavy atom effect.

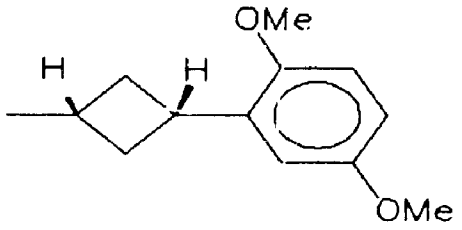
The measurements were made on solutions with an absorbance of ca. 1 at the Soret maximum which corresponds to roughly 10^{-5} M TTP. The Soret is the very intense absorption band at ca. 420 nm in free base porphyrins. The excitation wavelength was adjusted to the maximum of the Soret to obtain the greatest number of excited states in the shortest possible time. The emission was measured over a broad band of wavelengths; Corning cut off filter #2 - 58 which allowed only light of wavelength > 640 nm to pass was used in place of an emission monochromator. This broad band detection was necessary to accelerate the measurement process; using this

Figure 1-19: Compounds **62**, **108**, **109** and **112**

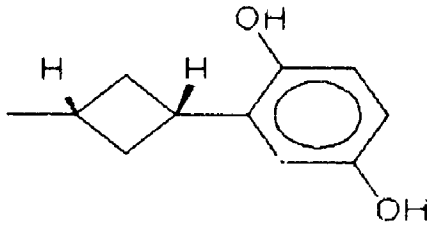


112 (TTP) R = CH_3

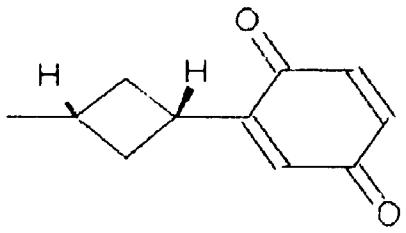
108 (P4DMB) R =



109 ($P4QH_2$) R =



62 (P4Q) R =



Notes for Table 1-2: a - all decays have at least 5×10^3 counts in the peak channel except as noted

b - A is the pre-exponential factor, it is a measure of the relative contribution of each lifetime to the composite decay

c - lifetimes in nanoseconds

d - 2.1×10^3 counts in the peak channel

e - 2.0×10^3 counts in the peak channel

f - 3.0×10^3 counts in the peak channel

Table 1-2: Fluorescence lifetimes of TTP, P4DMB, $P4QH_2$ and P4Q in various solvents[a]

Solvent	Compound	A[b]	τ[c]	χ^2
$CHCl_3$	TTP	1.000 +/- 0.003	8.99 +/- 0.02	1.24
	P4DMB	1.000 +/- 0.003	9.00 +/- 0.02	1.24
	$P4QH_2$	1.000 +/- 0.003	8.97 +/- 0.02	1.11
	P4Q[d]	0.008 +/- 0.000 0.992 +/- 0.054	7.59 +/- 0.18 0.35 +/- 0.02	1.12
CH_2Cl_2	TTP	1.000 +/- 0.003	9.11 +/- 0.02	1.29
	P4DMB	1.000 +/- 0.003	8.62 +/- 0.02	1.15
	$P4QH_2$	1.000 +/- 0.003	8.75 +/- 0.02	1.06
	P4Q	0.009 +/- 0.001 0.991 +/- 0.012	7.34 +/- 0.23 1.05 +/- 0.01	1.14
CH_3CN	TTP[e]	1.000 +/- 0.005	11.37 +/- 0.04	1.03
	P4DMB	1.000 +/- 0.001	10.46 +/- 0.01	0.97
	$P4QH_2$	1.000 +/- 0.003	11.65 +/- 0.03	0.99
	P4Q	0.089 +/- 0.114 0.911 +/- 0.110	8.39 +/- 1.80 5.31 +/- 0.22	1.07

(Table 1-2 cont.)

C_6H_6	TTP	1.000 +/- 0.003	11.68 +/- 0.03	1.09
	P4DMB	1.000 +/- 0.003	11.62 +/- 0.03	1.32
	$P4QH_2$	1.000 +/- 0.003	11.73 +/- 0.03	1.19
	P4Q	1.000 +/- 0.003	8.36 +/- 0.02	1.16
nC_4H_9OH	TTP[f]	1.000 +/- 0.003	12.05 +/- 0.03	1.05
	P4DMB	1.000 +/- 0.003	11.62 +/- 0.03	1.15
	$P4QH_2$	1.000 +/- 0.003	10.91 +/- 0.02	1.06
	P4Q	0.250 +/- 0.002 0.750 +/- 0.020	11.30 +/- 0.06 1.07 +/- 0.03	1.05
		0.394 +/- 0.003 0.606 +/- 0.018	11.43 +/- 0.05 1.25 +/- 0.04	1.14
C_6H_5CN	TTP	1.000 +/- 0.003	10.70 +/- 0.02	1.17
	P4DMB	1.000 +/- 0.002	10.85 +/- 0.02	1.04
	$P4QH_2$	0.687 +/- 0.003 0.313 +/- 0.119	11.32 +/- 0.04 0.78 +/- 0.21	0.87
	P4Q	0.093 +/- 0.001 0.907 +/- 0.014	10.88 +/- 0.08 1.08 +/- 0.02	1.22

procedure a typical decay profile could be collected in 3 - 4 hours. However, if the emission monochromator were used to eliminate most of the emitted light the collection time increased dramatically. Since the absorbance of the sample solutions was < 0.01 at all wavelengths in the 600 - 800 nm range there was therefore no need to use the emission monochromator, and its use would only have made measuring the decay profiles unnecessarily slow.

Fluorescence lifetime measurements were also made on P4DMB and $P4QH_2$ in the same solvents. The quality of fit of the calculated lifetimes to the real data was determined by the X^2 test, a statistical test based on the deviation of the real data from prediction. X^2 values outside the range 0.9 - 1.2 were suspect and the data analysis was repeated using a double exponential to fit the decay. If the X^2 value improved then the double exponential decay was retained to describe the data. The relative contribution of each exponential to the composite decay is measured by A the pre-exponential factor.

The lifetimes measured for P4DMB and $P4QH_2$, reported in Table 1-2, were very similar to the values obtained for TTP in the same solvent. This indicates that the presence of either the dimethoxyphenyl or hydroquinone side chain has little effect on the porphyrin S_1 state lifetime. The fact that a double exponential decay was required to adequately describe the decay profile of $P4QH_2$ in benzonitrile was attributed to contamination of the sample by P4Q. This may

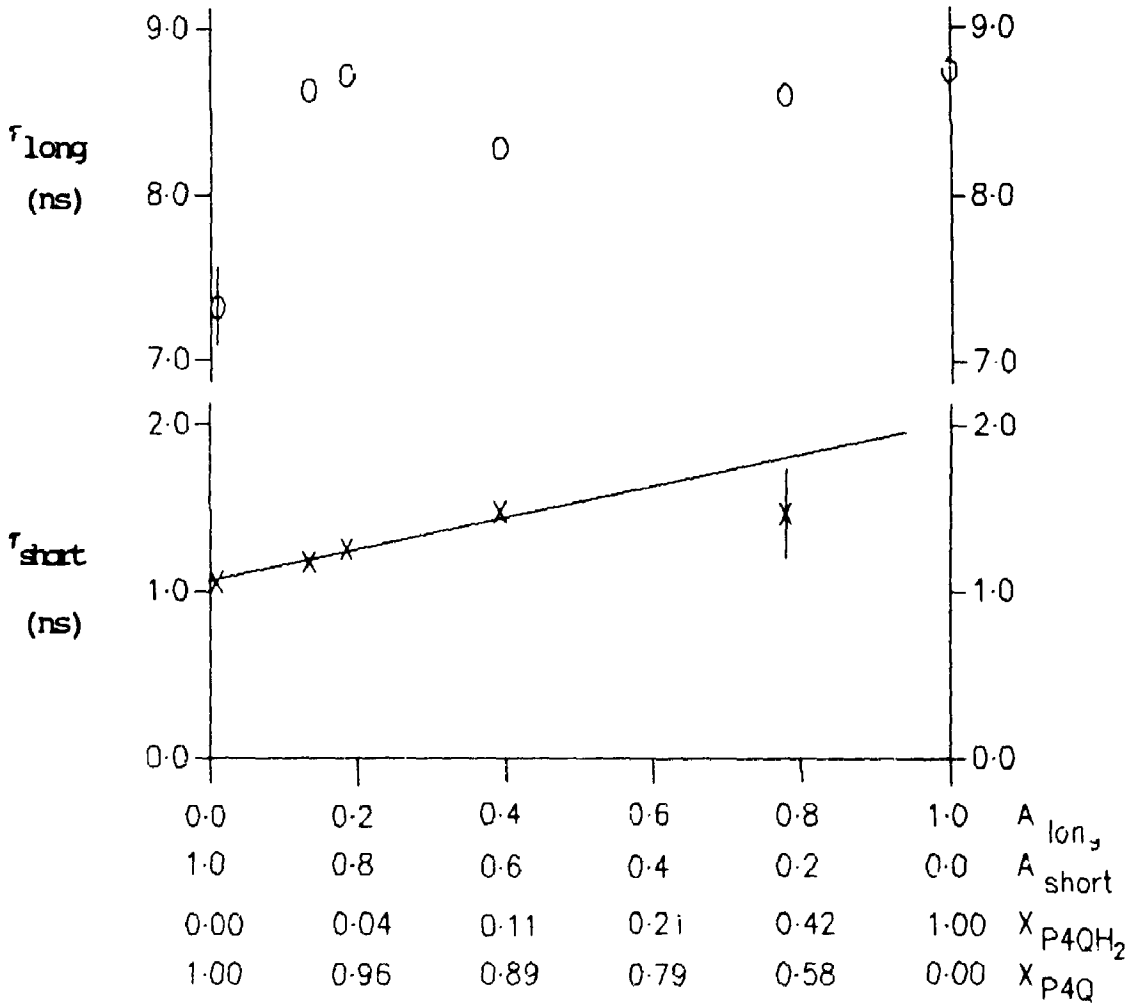
have arisen from oxidation of the hydroquinone by atmospheric oxygen. This was quite likely as this was the last sample to be measured and at the time the sample was prepared the $P4QH_2$ was ca. 48 hours old.

A series of small scale oxidations of $P4QH_2$ with lead dioxide gave the P4Q samples which were used for fluorescence measurements. The purity of each of these samples was not determined. It should be noted that the traces of impurity which were initially detected in the sample of P4Q used for characterization purposes would not affect the fluorescence results, even if it were present. This is because the concentrations of the samples on which the fluorescence measurements were made were all ca. 10^{-5} M; since the lifetimes of the fluorescing state were all ca. 10^{-9} s, then even if a quencher were present in a 1:1 ratio with P4Q and even if the quenching was diffusion controlled, the effect upon the fluorescence decay rate would be less than 0.1%.

As indicated in Table 1-2 it was found that double exponential decay kinetics were required to fit the fluorescence decay data for P4Q in all the solvents examined. This indicated that more than one fluorescing species was present and this was attributed to incomplete oxidation of the hydroquinone. The major and shorter lived component was attributed to the fluorescence decay of P4Q and the longer lived, minor component was attributed to residual $P4QH_2$. The fact that the longer lifetime is shorter than that measured on the pure $P4QH_2$ samples is an artifact of the computer

software and reflects the fact that $P4QH_2$ is present as a minor component in most cases. The process of fitting the data to a double exponential decay results in the incorporation of a larger error into the lifetime determined for a species if it is present as only a minor component. Furthermore, the error introduced is systematic and tends to bias the calculated lifetime towards that of the major component. Thus in this case the lifetimes determined from a double exponential decay fit to the data for a mixture of $P4QH_2$ and P4Q in which the later predominates to a large degree show an apparent shortening of the lifetime of $P4QH_2$. This was confirmed by analyzing the fluorescence decay profiles of a series of mixtures of varying proportions of P4Q and $P4QH_2$ in methylene chloride; the data are presented in Figure 1-20. It can be seen that contamination by $P4QH_2$ tends to increase the value of the short lifetime, attributed to P4Q, and this effect increases as the proportion of $P4QH_2$ is increased. The effect of P4Q on the lifetime of $P4QH_2$ was not evident unless the proportion of P4Q was very high, as is the case in most situations in Table 1-2. Thus the lifetime of $P4QH_2$ was only lowered when P4Q comprised more than 97% of the mixture. This can be understood if it is kept in mind that the decay profile was measured over ca. 40 ns; this corresponds to ca. 4 half lives for the $P4QH_2$ fluorescence, and roughly 20 half lives for P4Q fluorescence. Thus, unless the P4Q proportion is large, its contribution to the total fluorescence decay will not result in a perturbation of the

Figure 1-20: Plot of A vs τ for the long (O) and short (X) lifetimes of various $P4QH_2$ -- P4Q mixtures in CH_2Cl_2


τ long (ns)
9·0
8·0
7·0
τ short (ns)
2·0
1·0
0·0
0·0 0·2 0·4 0·6 0·8 1·0 A long
1·0 0·8 0·6 0·4 0·2 0·0 A short
0·00 0·04 0·11 0·2 i 0·42 1·00 X P4QH2
1·00 0·96 0·89 0·79 0·58 0·00 X P4Q

$P4QH_2$ fluorescence decay profile following the first few nanoseconds.

The decay profile of P4Q in benzene was adequately described by a single exponential even though there is presumably a small amount of $P4QH_2$ present fluorescing with a lifetime of ca. 11 ns. This was also an artifact of the software, which is incapable of resolving two closely spaced lifetimes when one is a minor contributor (53). Attempting to use two exponentials to describe the decay resulted in a poorer fit. Presumably the "true" rate of decay of P4Q in this solvent corresponds to a lifetime close to, but slightly less than the value of 8.4 ns determined. The decay of P4Q in acetonitrile was fit reasonably well by a single exponential decay, τ = 5.7 ns X^2 = 1.37. Although the fit was much better with a double exponential, τ = 5.3 and 8.4 ns X^2 = 1.07, this serves as an indication of the limits of the software.

The results in Table 1-2 for n-butanol suggest that a large concentration of $P4QH_2$ is apparently present in the solutions of P4Q. This result was found to be reproducible as indicated in Table 1-2 where duplicate measurements are shown. All the P4Q samples were prepared by PbO_2 oxidation of $P4QH_2$ in methylene chloride solution; following filtration the solvent was evaporated under a stream of nitrogen and the residue dissolved in the appropriate solvent. It was not reasonable to assume that the oxidation, which was at least 90% complete for all other samples, would only give 60-75%

conversion for both samples which were dissolved in n-butanol. The possibility of an oxidizable impurity in the n-butanol which was reducing the quinone in solution, was examined. The n-butanol used was a middle cut of a constant boiling fraction, bp = 117°C. It is therefore unlikely, although not impossible for such an impurity to be present. As will be revealed below, the steady state fluorescence intensity for the second n-butanol sample, for which A_{short} = 0.606, was less than that of the first n-butanol sample, for which A_{short} = 0.750. As will be discussed later, the steady state fluorescence intensity should be quenched for P4Q relative to $P4QH_2$. Yet in these two samples the steady state fluorescence intensity appears to increase as the oxidation of the sample becomes more complete. Clearly, this should not be the case. It should be noted that n-butanol is the only solvent studied capable of hydrogen bonding with the quinone. The possibility of some previously unreported interference to electron transfer caused by solvation of the quinone cannot be ruled out.

The shorter fluorescence lifetime of P4Q relative to $P4QH_2$ is attributed to electron transfer from the porphyrin S_1 state to the quinone, giving rise to a charge separated state. This new radical cation/radical anion state is designated $P^{+\cdot}Q^{-\cdot}$. The energy level of this new state was not determined; however by comparison with other porphyrin quinone systems it can be assumed to be ca. 1.4 eV (32 Kcal) above the ground state (5d). From the fluorescence spectra it was

determined that the S_1 state is 1.90 eV (44 Kcal) above the ground state.

Electron transfer in P4Q provides the S_1 state with a decay pathway, rate constant k_{et}, not accessible in the precursor species P4DMB and $P4QH_2$. This is shown in Figure 1-21. Equation 1-3 describes the lifetime of the S_1 state of P4Q (τ_1). Equation 1-4, which is a restatement of equation 1-2 on page 148, describes the lifetime of the S_1 state of $P4QH_2$ (τ_2).

$$\tau_1 = (k_f + k_{ic} + k_{isc} + k_{et})^{-1} \quad - (1\text{-}3)$$

$$\tau_2 = (k_f + k_{ic} + k_{isc})^{-1} \quad - (1\text{-}4)$$

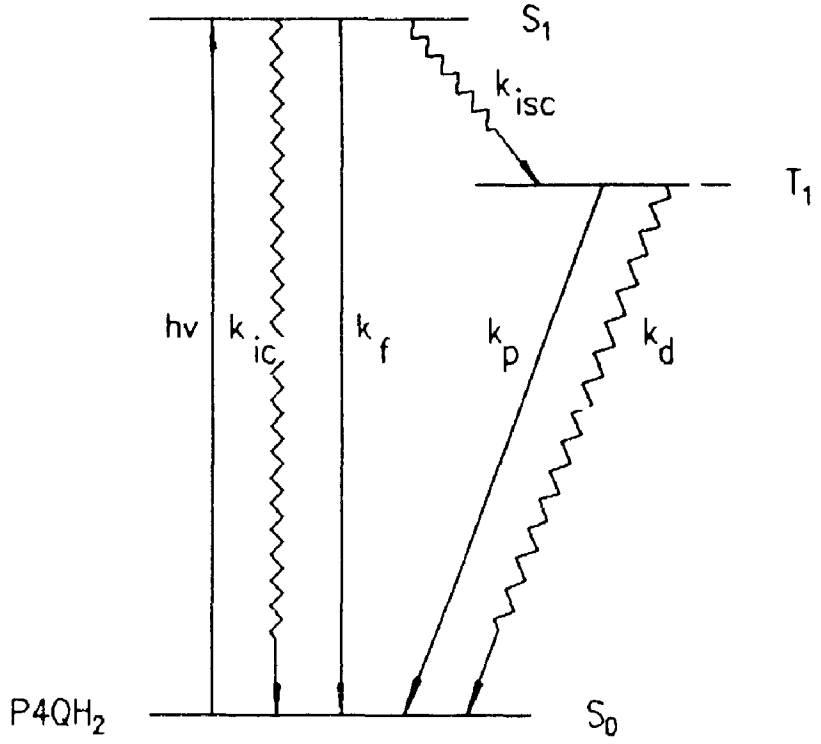
If the reasonable assumption is made that the oxidation of the hydroquinone to the quinone will have no effect on the rate constants k_f, k_{ic} and k_{isc} for the decay of the porphyrin S_1 state then equation 1-5 can be written.

$$k_{et} = \tau_1^{-1} - \tau_2^{-1} \quad - (1\text{-}5)$$

This equation, which describes the electron transfer rate constant in terms of measurable properties, is the basis for the k_{et} values given in Table 1-3. These values will be discussed further below.

Just as the fluorescence lifetime of P4Q was reduced relative to that of $P4QH_2$, so too was the steady state

Figure 1-21: Jablonski diagrams for $P4QH_2$ and P4Q, ignoring the $S_0 - S_2$ transition


S1
k isc
T1
hv
k ic
k f
k p
k d
P4QH2
S0

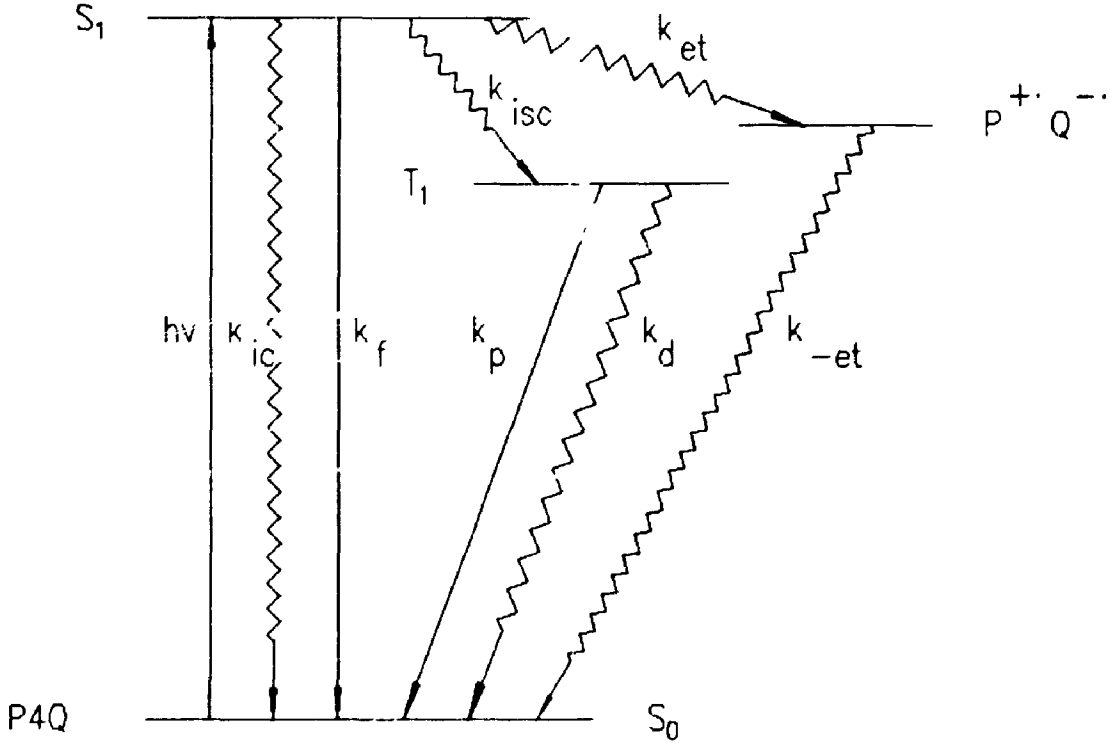

S1
k et
k isc
P+· Q−·
T1
hv
k ic
k f
k p
k d
k −et
P4Q
S0

Table 1-3: k_{et} values, derived from lifetime measurements, for P4Q in various solvents

Solvent	k_{et} (s^{-1})
$CHCl_3$	$2.75 \pm 0.16 \times 10^9$
CH_2Cl_2	$8.38 \pm 0.09 \times 10^8$
CH_3CN	$1.02 \pm 0.08 \times 10^8$
C_6H_6	$3.44 \pm 0.05 \times 10^7$
nC_4H_9OH	$8.43 \pm 0.26 \times 10^8$
C_6H_5CN	$8.38 \pm 0.17 \times 10^8$

fluorescence intensity. This is to be expected since fluorescence competes with electron transfer in P4Q. The fluorescence quantum yields were determined and are reported in Table 1-4. These values were determined by comparing the total integrated fluorescence intensity of dilute solutions of TTP, P4DMB, $P4QH_2$, and P4Q with that of a dilute solution of 5-(p-carboxyphenyl)-10,15,20-tritolyl porphyrin (TTPa) in methylene chloride. The quantum yield of fluorescence of TTPa in methylene chloride was measured against that of tetraphenylporphyrin (TPP) in aerated benzene. The absolute quantum yield of fluorescence, ϕ_f, of TPP in aerated benzene has been reported as 0.11 (54). Using this as a standard allowed the calculation of the absolute quantum yields of fluorescence of TTPa, TTP, P4DME, $P4QH_2$ and P4Q in the solvents of interest. This calculation is based on the fact that the intensity of fluorescence emission is proportional to the product of the absorbance and the fluorescence quantum yield if the absorbance is low. The requirement for absorbance to be low can be seen by examining equation 1-6.

$$\phi_f = (I_f A_s \phi_{fs}) (I_{fs} A)^{-1} \qquad - (1\text{-}6)$$

This equation, which relates the fluorescence quantum yield of a species to that of a standard, designated by the subscript s, is a truncation of the power series expansion of equation 1-7. This truncation is valid only if the absorbance of all solutions is kept small (ie. $A \leq 0.05$). For this

Table 1-4: Fluorescence quantum yields[a] for TTP, P4DMB, $P4QH_2$ and P4Q in various solvents

Solvent	Compound	ϕ_f[b]
$CHCl_3$	TTP	0.091
	P4DMB	0.071
	$P4QH_2$	0.065
	P4Q	0.0043
CH_2Cl_2	TTP	0.10
	P4DMB	0.092
	$P4QH_2$	0.078
	P4Q	0.014
CH_3CN	TTP	0.14
	P4DMB	0.12
	$P4QH_2$	0.11
	P4Q	0.055
C_6H_6	TTP	0.12
	P4DMB	0.11
	$P4QH_2$	0.10
	P4Q	0.084
	P4Q	0.089
nC_4H_9OH	TTP	0.12
	P4DMB	0.11
	$P4QH_2$	0.097
	P4Q	0.049
	P4Q	0.037
C_6H_5CN	TTP	0.13
	P4DMB	0.11
	$P4QH_2$	0.12
	P4Q	0.024

a - ϕ_f values based on TTP in aerated benzene, $\phi_f = 0.11$ (54), TTPa in CH_2Cl_2, $\phi_f = 0.082$, was used as an internal check

b - uncertainty in ϕ_f values is estimated to be ca. 5% for the TTP, P4DMB and $P4QH_2$ solutions
the ϕ_f values measured for the P4Q solutions are strongly dependant on the level of contamination by $P4QH_2$, the presence of as little as 2% $P4QH_2$ can result in as much as a 30% reduction in the calculated value of ϕ_f

reason dilute solutions of the porphyrins (concentration ca. 5×10^{-7} M) were used for measurement of the fluorescence quantum yields.

$$\phi_f = (I_f\ (1 - 10^{-A_s})\ \phi_{fs})\ (I_{fs}\ (1 - 10^{-A}))^{-1} \quad - (1\text{-}7)$$

The quantity I_f is the integrated total fluorescence emission of the sample. The quantity A is the absorbance of the sample at the excitation wavelength.

The excitation wavelength varied slightly from solvent to solvent, but was always adjusted to the wavelength of maximum absorbance of the Soret band. This adjustment would not be necessary if the spectrofluorimeter had an infinitely thin excitation band width. However, as the excitation band width was 2 nm this adjustment was necessary to ensure that the measured absorbance values were proportional to the integrated absorbance of the sample over the excitation band width and in turn that the ratio I_f/A was proportional to ϕ_f.

It should be noted that for the purpose of calculating k_{et} the absolute values of ϕ_f are not as important as the relative values. This can be seen by consideration of equations 1-8, 1-9 and 1-10. Equation 1-8 defines the quantum yield of fluorescence for P4Q (ϕ_{f_1}) and equation 1-9 defines it for $P4QH_2$ (ϕ_{f_2}), Figure 1-21. Again, assuming that oxidation of the hydroquinone to the quinone will have no effect on the rate constants k_f, k_{ic} and k_{isc} then equation

1-10 can be written, where τ_2 is the fluorescence lifetime of $P4QH_2$.

$$\phi_{f_1} = k_f \times (k_f + k_{ic} + k_{isc} + k_{et})^{-1} \quad - (1\text{-}8)$$

$$\phi_{f_2} = k_f \times (k_f + k_{ic} + k_{isc})^{-1} \quad - (1\text{-}9)$$

$$k_{et} = ((\phi_{f_2} / \phi_{f_1}) - 1) \times (\tau_2)^{-1} \quad - (1\text{-}10)$$

The decrease in ϕ_f from $P4QH_2$ to P4Q in most solvents was substantial. The presence of any residual $P4QH_2$ in the P4Q samples would therefore be expected to have a major effect. Residual $P4QH_2$ was detected in the P4Q samples by fluorescence lifetime measurements, as discussed earlier. Therefore, the k_{et} values determined from steady state fluorescence measurements and reported in Table 1-5 should be regarded only as lower limits. This is consistent with the large discrepancy in the k_{et} values obtained from steady state measurements and from lifetime measurements. Although the absolute values of k_{et} calculated from the steady state fluorescence measurements are different than those from the lifetime measurements the trend from solvent to solvent is constant.

Table 1-5: k_{et} values, derived from quantum yield measurements, for P4Q in various solvents

Solvent	k_{et}[a] (s^{-1})	(k_{et}[b] (s^{-1}))
$CHCl_3$	1.6 +/- 0.8 x 10^9	(2.75 +/- 0.16 x 10^9)
CH_2Cl_2	5.2 +/- 2.6 x 10^8	(8.38 +/- 0.09 x 10^8)
CH_3CN	8.6 +/- 4.3 x 10^7	(1.02 +/- 0.08 x 10^8)
C_6H_6	1.6 +/- 0.8 x 10^7	(3.44 +/- 0.05 x 10^7)
nC_4H_9OH	1.5 +/- 0.8 x 10^8	(8.43 +/- 0.26 x 10^8)
C_6H_5CN	3.5 +/- 1.8 x 10^8	(8.38 +/- 0.17 x 10^8)

a - the calculated value of k_{et} is highly dependant upon the level of contamination by $P4QH_2$, adjusting the calculations to reflect the presence of as little as 2% $P4QH_2$ results in as much as a 50% increase in the calculated value of k_{et}

b - from table 1-3, values based on fluorescence lifetime measurements

iii - Comparison of P4Q with Other Porphyrin Quinone Systems

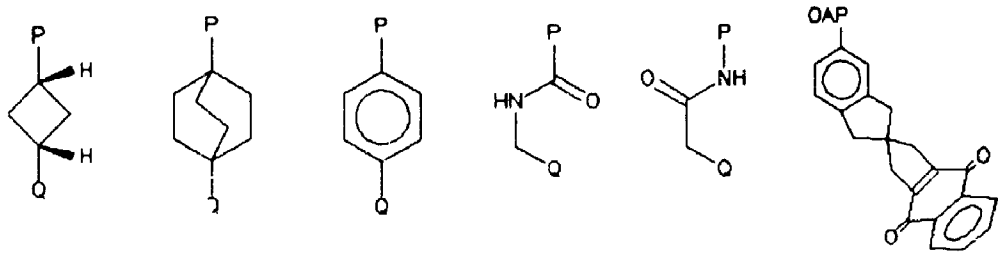
The forward electron transfer rate constants measured for P4Q are compared with those for other systems with a similar donor acceptor separation in Table 1-6. The data indicate that electron transfer in P4Q is surprisingly rapid.

For the bicyclooctane linked species 33, electron transfer is thought to occur via a superexchange mechanism (15). This superexchange mechanism is mediated by the valence band of molecular orbitals, and can be viewed as a hole transfer mechanism. Since the linking units of both species 33 and P4Q are composed only of sp^3 hybridized carbon atoms, the same mechanism might be expected to operate. However, electron transfer in P4Q occurs from two to fifty-seven times faster than it does in the bicyclooctane linked species 33. This may suggest that a superexchange mechanism is not operating for 62. However, it should be noted that electron transfer in 33 occurs through 5 bonds, but only 4 bonds in 62, and this may also account for the relatively faster electron transfer rate.

Electron transfer in P4Q can also be thought of as occurring via the conduction band of molecular orbitals; ie through the antibonding orbitals. The ring strain of the cyclobutane ring may cause a lowering of the energy of these antibonding orbitals relative to those in 33 such that they are accessible as a pathway for electron transfer.

The possibility that electron transfer occurs via the antibonding molecular orbitals may also account for the

Table 1-6: Comparison of P4Q k_{et} values with those for other linke porphyrin-quinone species



Compound	62	33	26	14	49	48
Solvent						
$CHCl_3$	27.	---	---	22.	---	---
CH_2Cl_2	8.4	0.153	27.	8.0	99.	4.3
CH_3CN	1.0	ca. 0.000	57.	0.48	---	---
C_6H_6	0.34	0.150	3.8	1.8	---	---
nC_4H_9OH	8.4	0.146	---	2.1	---	---
C_6H_5CN	8.4	---	---	3.9	---	---
Reference		16	13	10a	25	24

note: all k_{et} values are in units of 10^8 s^{-1}

differences in electron transfer rates between species 14, 26, 33, 49 and P4Q. The rate constant in methylene chloride, the only solvent in which k_{et} values for all species are known, changes by ca. three orders of magnitude within this series of compounds. The fastest of these rates is observed for compound 49. This may be the result of homoconjugation between the carbonyl pi-system and that of the quinone ring. The antibonding orbitals associated with this homoconjugated system would be relatively low in energy and therefore readily accessible for electron transfer. This relatively low energy level is reflected in a large electron transfer rate constant. The antibonding orbitals associated with the phenyl linkage, species 26, would also be easily accessible for electron transfer. This is once again reflected in a large value for k_{et}. The remaining compounds in this series do not possess fully conjugated pi systems. The connecting linkage of compound 14 possess a pi system in conjugation with that of the porphyrin but not with the quinone. This conjugation although incomplete still has an effect on the energy level of the antibonding orbitals, lowering them relative to those of a fully saturated linkage. This effect coupled with the fact that the porphyrin and quinone are connected through four bonds in 14 may be used to rationalize the observed rates of electron transfer in 14 relative to those of the fully saturated, bicyclooctane linked species, 33, in which the connection is through five bonds. The similarity of the rate constants for photo induced intramolecular electron transfer

in species **14** and P4Q may be rationalized by realizing the P4Q linkage is only four bonds and that the ring strain of the cyclobutane ring will cause a lowering of the energy level of the antibonding orbitals relative to those of a strain free saturated ystem. It is therefore not unreasonable that species **14** and P4Q have similar values of k_{et}.

Comparison of the rate constant for species **48** with those for P4Q is dangerous. In both of these species the linking units are composed only of sp^3 hybridized carbon atoms and in both 4 bonds separate the donor and acceptor. However, species **48** has an octaalkyl porphyrin as the donor, rather than a tetraphenyl porphyrin, and a naphthoquinone, rather than a benzoquinone, as the acceptor. Both these differences would favour electron transfer. The fact that the rate is similar is therefore difficult to interpret.

The solvent effects observed for P4Q are consistent with Marcus theory in that this theory predicts the rate of electron transfer to be dependant on the solvent contribution to the reorganization energy. The solvent contribution to the reorganization energy is in turn dependant on the square of the refractive index, n, and dielectric constant, ϵ. For a given donor acceptor system in various solvents equation 1-11 describes the solvent dependence predicted by Marcus theory.

$$-\ln(k_{et}) \propto (n^{-2} - \epsilon^{-1}) \qquad - (1\text{-}11)$$

The data are presented in Table 1-7 and plotted in Figure 1-22. This figure illustrates a high level of correlation between theory and observation for five of the six solvents. The failure of the benzene data (which is seen close to the vertical axis) to fall close to the line of best fit obtained from the other solvents was also observed for compound **14**. This behavior and that of other non-polar solvents was rationalized by Schmidt (54) as follows: an assumption central to equation 1-11 is that the solvent cage containing the ground state donor acceptor species has the same dielectric constant as the bulk solvent. The induced dipoles in the solvent cage around the ground state donor acceptor molecule will raise the local dielectric constant significantly, resulting in the assumption not being valid. Thus, for solvents of low dielectric constant, the use of the bulk solvent dielectric constant will result in the term ϵ^{-1} being too large.

iv - Conclusions and Suggestions for Future Work

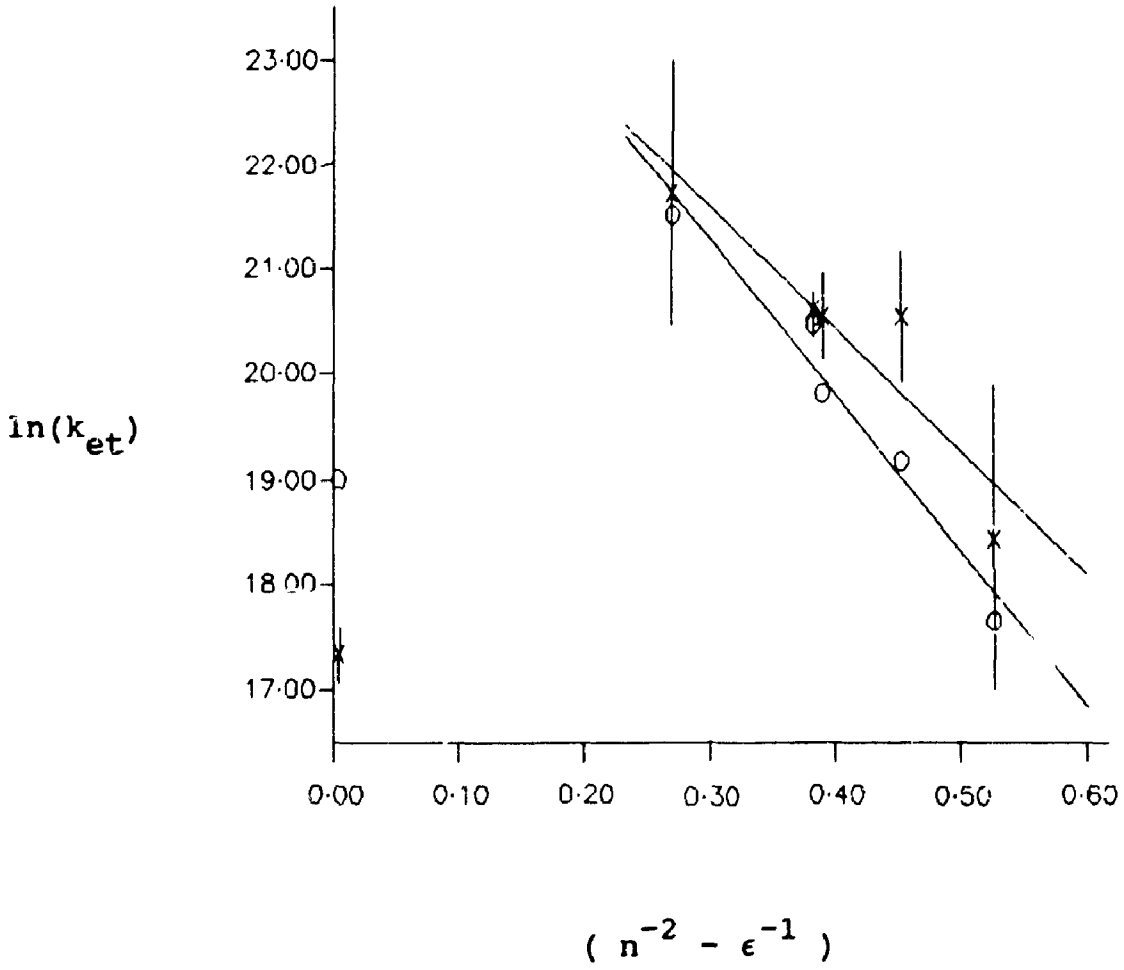
The cis cyclobutane linked porphyrin quinone species **62** was synthesised and characterized both as a new organic compound and as a species capable of exhibiting intramolecular photochemical electron transfer. This electron transfer was found to occur at a rate faster than anticipated by comparison with other models. This relative ease of electron transfer within this system was rationalized as due to the ring strain associated with the cyclobutane ring. The solvent dependence

Table 1-7: Solvent Dependence of k_{et} for Compound 62 (P4Q)

Solvent	n	ϵ	$n^{-2} - \epsilon^{-1}$	$\ln(k_{et})^a$
$CHCl_3$	1.446	4.81	0.2704	21.73 +/- 1.26
CH_2Cl_2	1.424	9.14	0.3837	20.55 +/- 0.22
C_6H_5CN	1.527	25.6	0.3898	20.55 +/- 0.42
nC_4H_9OH	1.399	17.5	0.4538	20.55 +/- 0.63
CH_3CN	1.344	37.5	0.5269	18.44 +/- 1.45
C_6H_6	1.501	2.27	0.0033	17.35 +/- 0.25

a - k_{et} values from fluorescence lifetime measurements (table 1-3)

Figure 1-22: Plot of ($n^{-2} - \epsilon^{-1}$) vs ln (k_{et}) for P4Q (X) and **14** (O)


ln(k_et)
23·00
22·00
21·00
20·00
19·00
18·00
17·00
0·00
0·10
0·20
0·30
0·40
0·50
0·60
(n^-2 - ε^-1)

of the electron transfer rate constant was found to be in agreement with the trends predicted by Marcus theory.

Unfortunately, the trans isomer 63 was not accessible via the synthetic pathway to the cis isomer. The synthesis of the trans isomer, although a major undertaking, would allow for a very interesting comparison.

Equally interesting would be comparison of 62 with the next homologue 70 (Figure 23), in which the connecting linkage would be a spirocycloheptane unit. A comparison such as this has been made for a system in which the donor was a ruthenium center in the +2 oxidation state and the acceptor was a ruthenium in the +3 oxidation state (55); however there is little similarity between this class of compounds and the porphyrin quinone compounds.

of/de 3

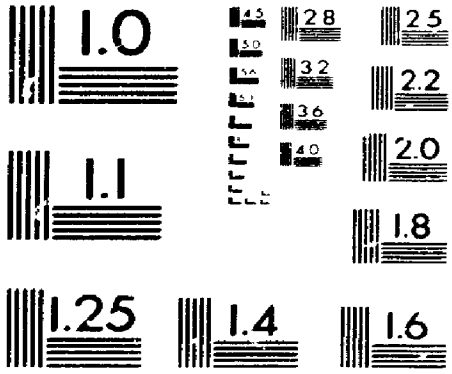
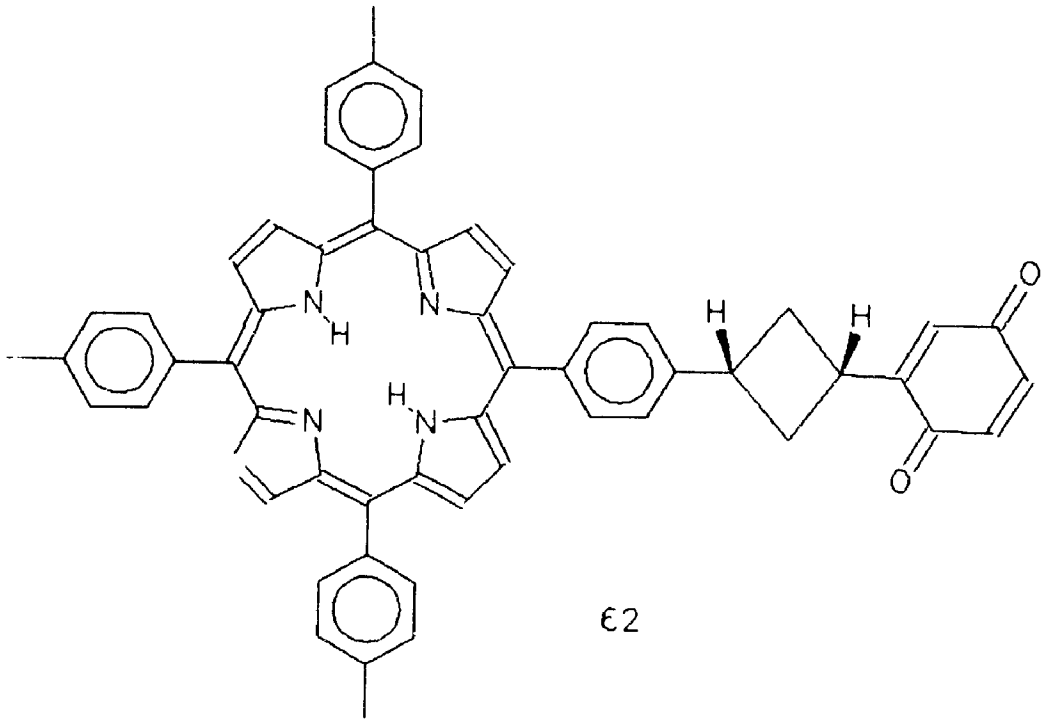
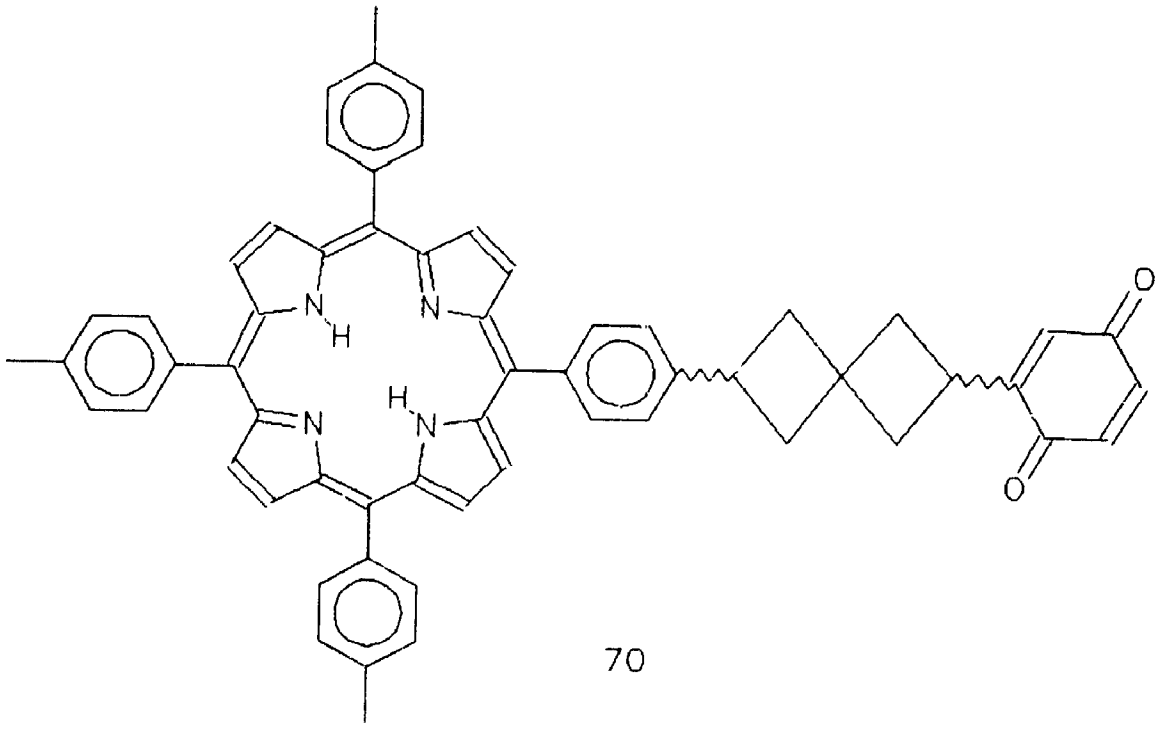


Figure 1-23: Compounds **62** and **70**



€2



70

(C) EXPERIMENTAL

General

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Boiling points are also uncorrected. Routine ^{1}H NMR spectra were recorded on either a Varian T-60 or EM-360 instrument. ^{1}H NMR spectra used for characterization purposes were recorded on either a Varian XL-100 or XL-200 instrument. ^{13}C NMR spectra were recorded on a Varian XL-300 instrument. DEPT and APT spectra, also run on a Varian XL-300 instrument, were used to determine the multiplicities of the carbon signals. ^{1}H-^{13}C heteronuclear correlation spectra were run on a Varian XL-300 instrument. Infrared spectra were recorded on either a Beckman IR-4250 or a Bruker IFS-32 instrument. Ultra-Violet and visible spectra were recorded on either a Cary 219, a Hewlett-Packard 8450, or a Shimadzu UV160 instrument. Steady state fluorescence emission spectra were recorded on either a Perkin-Elmer MPF4 or 650-40 instrument. Fluorescence lifetimes were measured with a PRA International Inc. 3000 nanosecond spectrofluorimeter. A PRA model 510 hydrogen flashlamp was used as the excitation source. Mass spectra were recorded on either a Varian MAT-311A or a Finnigan MAT-8230 instrument, both run at 70 ev with direct inlet (except as noted). GC-MS were run on a Finnigan MAT-8230 instrument run at 70 ev using a 30 meter DB5 Megabore column. Gas-liquid chromatography (GLC) was performed on either a Varian 2400 or a Hewlett-

Packard 5880 instrument (column type and temperature conditions are reported where it is relevant).

Solvents were BDH or Fischer reagent grade, which were used as supplied, except tetrahydrofuran, which was dried over sodium/benzophenone. Dry ether refers to one of Baker, BDH or Fischer anhydrous grade ether, which was used as supplied from freshly opened bottles. Benzene was dried by storing it over 4A molecular sieves. Solvents for fluorescence measurements were either Fischer spectroscopic grade or a middle cut of the constant boiling fraction from a fractional distillation of the reagent grade solvent. All fluorescence solvents were checked for fluorescent impurities prior to use. Halogenated fluorescence solvents were stored over anhydrous sodium carbonate.

Alkyl lithium reagents, purchased from Aldrich, were assumed to be the strength stated on the bottle, provided they contained little or no precipitate. All other reagents were purchased from one of Aldrich, BDH or Fischer and were used as supplied, except as noted.

Oxidation of $P4QH_2$ to P4Q (62)

A solution prepared by dissolving ca. 3 mg of $P4QH_2$ in ca. 5 ml of methylene chloride was added to a 16 x 150 test tube containing ca. 0.2 gm of lead dioxide and shaken by hand for ca. 20 minutes. The reaction mixture was filtered through a 1.2 μm Millipore filter. The residue was washed with ca. 2 ml of fresh methylene chloride, which was added to the

filtrate. The filtrate was evaporated to dryness on the rotary evaporator. The crude product was purified by preparative thick layer chromatography on non-fluorescent silica, benzene as eluent. ^{1}H NMR ($CDCl_3$): 2.40 (2H,dt,J=11,9 Hz), 2.69 (9H,s), 2.96 (2H,dt,J=11,7 Hz), 3.64 (1H,tt,J=9,7 Hz), 3.91 (1H,tt,J=9,7 Hz), 6.70 (1H,s (broad)), 6.78 (2H,m), 7.53 (6H,d,J=8 Hz), 7.55 (2H,d,J=8 Hz), 8.08 (6H,d,J=8 Hz), 8.13 (2H,d,J=8 Hz), 8.83 (8H,s); ^{13}C NMR ($CDCl_3$): 21.6 (CH_3), 30.9 (CH), 35.7 (CH_2), 36.5 (CH), 124.7, 127.5, 128.4, 131.0, 134.6, 134.7, 136.4, 137.0 (aromatic CH), 119.8, 120.2, 120.2, ca. 131 (broad), 137.4, 139.3, 140.3, 143.8, 151.7 (aromatic C), 187.6, 188.0 (carbonyl); observed m/e: 818 (80%), 816 (20%, unstable), 682 (100%); exact mass (for P4QH$_2$) $C_{57}H_{46}N_4O_2$ calculated 818.36205, observed 818.36184

^{1}H NMR ($CDCl_3$) decoupling, considering only the multiplets at 2.40, 2.96, 3.64 and 3.91 ppm. Saturation of the signal at 2.40 ppm resulted in the 3.64 and 3.91 ppm signals collapsing to triplets, J = 7 Hz, and the 2.96 ppm signal collapsing to a crude triplet, J = 7 Hz. Saturation of the signal at 2.96 ppm resulted in the 3.64 and 3.91 ppm signals collapsing to triplets, J = 9 Hz, and the 2.40 ppm signal collapsing to a crude triplet, J = 9 Hz. Saturation of the 3.64 ppm signal had no effect on the 3.91 ppm signal. The 2.40 ppm signal collapsed to crude doublet of doublets, J = 9 and 11 Hz. The 2.96 ppm signal also collapsed to a crude doublet of doublets, J = 7 and 11 Hz. Saturation of the 3.91 ppm signal had no effect on the 3.64 ppm signal. The

2.40 ppm signal collapsed to a crude doublet of doublets, J = 9 and 11 Hz. This crude doublet of doublets was exactly superimposable on the crude doublet of doublets obtained by saturation of the 3.64 ppm signal. The 2.96 ppm signal also collapsed to a crude doublet of doublets, J = 7 and 11 Hz. Again, this crude doublet of doublets was exactly superimposable on the crude doublet of doublets obtained from saturation of the 3.64 ppm signal.

cis 4-(3-(2,5-Dimethoxyphenyl)cyclobutyl)benzaldehyde (64)

To a 25 ml pear flask equipped with a reflux condenser and a magnetic stirrer was added 30.4 mg (0.08 mmol) of cis 1-(2,5-dimethoxyphenyl)-3-(4-(4,4-dimethyl-2,6-dioxanyl) phenyl)cyclobutane **106** and 10 ml of acetone. A few crystals of p-toluene sulfonic acid were added. After 2 hours reflux, TLC indicated complete clean conversion. The reaction mixture was diluted with 50 ml of ether and washed with saturated sodium bicarbonate solution (25 ml), water (3 x 50 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator. Yield 29.5 mg of a yellow oil. The crude product was purified by preparative thick layer chromatography on silica, 20% ether in hexanes as eluent. Yield 17.1 mg (73%) of a colourless oil. ^{1}H NMR ($CDCl_3$): 2.22 (2H,dtt,J=11,11,2.5 Hz), 2.81 (2H,dtq,J=8,7.5,2.5 Hz), 3.56 (1H,tt,J=9,7.5 Hz), 3.69 (1H,tt,J=9,7.5 Hz), 3.76 (3H,s), 3.77 (3H,s), 6.67 (1H,dd,J=8,3 Hz), 6.76 (1H,d,J=8 Hz), 6.77 (1H,d,J=3 Hz), 7.37 (2H,d,J=8 Hz), 7.80 (2H,d,J=8 Hz), 9.95

(1H,s); ^{13}C NMR ($CDCl_3$): 31.5 (CH), 36.0 (CH_2), 36.6 (CH), 55.7 (CH_3), 55.9 (CH_3), 110.5, 111.1, 114.0, 127.2, 129.9 (aromatic CH), 134.3, 134.5, 151.8, 153.0, 153.6 (aromatic C), 192.0 (carbonyl); ir (film): 1697 cm^{-1}; observed m/e: 296 (21%), 164 (100%), 149 (31%); exact mass for $C_{19}H_{20}O_3$ calculated 296.14123, observed 296.14066

2-(2,5-Dimethoxyphenyl)-1,3-propanediol ditosylate (66)

To a 100 ml round bottom flask equipped with a magnetic stirrer was added 1.6 gm (7.5 mmol) of 2-(2,5-dimethoxy phenyl)-1,3-propane-diol 72, 4.2 gm (22.1 mmol) of p-toluene sulfonyl chloride (recrystallized from petroleum ether), and 30 ml of dry pyridine. This mixture was stirred at room temperature until homogeneous (ca. 5 min). The reaction vessel was then sealed and stored in the refrigerator over night. The reaction mixture was poured onto crushed ice (30 gm) and extracted with ether (3 x 30 ml). The ether extracts were washed with dilute hydrochloric acid (30 ml of 2N), followed by water (2 x 30 ml), dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary evaporator. Yield 3.4 gm (87%) of a white crystalline solid. Recrystallization of a small portion of this material from ether/30-60 petroleum ether yielded a white solid, mp = 86-87°C. ^1H NMR ($CDCl_3$): 2.44 (6H,s), 3.58 (1H,q,J=6 Hz), 3.60 (3H,s), 3.70 (3H,s), 4.22 (4H,d,J=7 Hz), 6.51 (1H,d,J=3 Hz), 6.64 (1H,d,J=8 Hz), 6.72 (1H,dd,J=8,3 Hz), 7.29 (4H,d,J=8 Hz),

7.66 (4H,d,J=8 Hz); ir (Nujol): 1368, 1175 cm^{-1}; observed m/e: 520 (100%), 348 (42%), 91 (66%); exact mass for $C_{25}H_{28}O_8S_2$ calculated 520.12252, observed 520.12243

Ethyl 2,5-dimethoxyphenyl-acetate (68)

To a 100 ml round bottom flask equipped with a reflux condenser and a magnetic stirrer was added 15.1 gm (77 mmol) of 2,5-dimethoxyphenyl-acetic acid (purchased from Aldrich and used as supplied) and 60 ml of thionyl chloride. The thionyl chloride had previously been distilled from triphenyl phosphite (ca. 15% v/v). The reaction mixture was refluxed until it was homogeneous (ca. 5 min). The reflux condenser was then replaced with a condenser set for distillation and the excess thionyl chloride was distilled out. Dry benzene (30 ml) was added and distilled out. This was repeated three times to ensure complete removal of traces of thionyl chloride. A fourth portion of dry benzene was then introduced. The resulting benzene solution was added dropwise to an ice cooled solution of absolute ethyl alcohol (150 ml) and triethylamine (15 ml). After 10 minutes, water (50 ml) was added. The reaction mixture was then extracted with ether (3 x 50 ml). The ether extracts were washed with water (50 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator.

The crude product was distilled under reduced pressure, bp = 139-140°C at 2 mm Hg (literature bp = 162-165°C at 8 mm

Hg (56)). Yield 12.8 gm (78%) of a colourless oil. ^1H NMR ($CDCl_3$): 1.25 (3H,t,J=7 Hz), 3.59 (2H,s), 3.76 (3H,s), 3.77 (3H,s), 4.16 (2H,q,J=7 Hz), 6.78 (3H,s); ir (film): 1740 cm^{-1}; observed m/e: 224 (81%), 151 (100%), 121 (67%); exact mass for $C_{12}H_{16}O_4$ calculated 224.10484, observed 224.10453

Ethyl 2-(2,5-dimethoxyphenyl)malonate (71)

To a 250 ml three necked round bottom flask equipped with a dropping funnel, a reflux condenser capped with a nitrogen inlet, a magnetic stirrer and a septum cap was added 10.5 ml (75 mmol) of diisopropyl amine and 75 ml of dry tetrahydrofuran. The flask was cooled in a ice/salt bath. 30 ml (75 mmol) of n-butyl lithium (2.5M in hexanes) was added dropwise. After 10 min a solution of 15.3 gm (68 mmol) of ethyl 2,5-dimethoxyphenyl-acetate **68** in 50 ml of dry tetrahydrofuran was added dropwise to this lithium diisopropylamide solution. The reaction flask was slowly warmed to room temperature. A stream of carbon dioxide gas (from subliming dry ice) was bubbled through the solution for 15 min. Water (50 ml) and dilute hydrochloric acid (20 ml of 10%) were then added. The reaction mixture was extracted with chloroform (3 x 50 ml). The chloroform extracts were extracted with saturated sodium bicarbonate solution (3 x 50 ml). This aqueous layer was then acidified with dilute hydrochloric acid and extracted with ether (3 x 50 ml). The ether extracts were washed with water

(2 x 50 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator. Yield 9.5 gm (52%) of a yellow crystalline solid. Recovered ethyl 2,5-dimethoxyphenyl-acetate, 6.2 gm, accounted for 85% of the missing mass.

The crude product was twice recrystallized from methylene chloride/30-60 petroleum ether. Yield 4.8 gm (44% based on converted starting material) of a white solid, mp = 89-90°C (literature mp = 75°C (57)). ^{1}H NMR ($CDCl_3$): 1.25 (3H,t, J=7 Hz), 3.77 (3H,s), 3.78 (3H,s), 4.25 (2H,q,J=7 Hz), 4.92 (1H,s), 6.84 (2H,m), 6.93 (1H,m); ir (Nujol): 1775, 1730, 1720 cm^{-1} (literature ir (KBr): 1760, 1735 cm^{-1} (57)); observed m/e: 268 (10%), 224 (100%), 151 (71%); exact mass for $C_{13}H_{16}O_6$ calculated 268.09466, observed 268.09439

2-(2,5-Dimethoxyphenyl)-1,3-propane-diol (72)

To a 500 ml three necked round bottom flask equipped with a dropping funnel, a reflux condenser capped with a nitrogen inlet and a magnetic stirrer was added 7.1 gm (187 mmol) of lithium aluminum hydride and 250 ml of dry ether. A solution of 10.0 gm (37 mmol) of ethyl 2-(2,5-dimethoxyphenyl)malonate 71 in 50 ml of dry ether was slowly added. The rate of addition was controlled so as to maintain a gentle reflux. 15 minutes after the addition was complete, ethyl acetate was added to destroy excess lithium aluminum hydride. The solution was then cooled in an ice bath and 200 ml of 10% sulphuric acid was added. The reaction mixture was then

extracted with ether (3 x 100 ml). The ether extracts were washed with water (2 x 50 ml), dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary evaporator. Yield 7.1 gm (90%) of a yellowish oil which slowly crystallized. The crude diol was recrystallized from ether/30-60 petroleum ether. Yield 3.7 gm (47%) of a white crystalline solid, mp = 73-74°C. ^{1}H NMR ($CDCl_3$): 2.62 (2H,s), 3.49 (1H,m), 3.75 (3H,s), 3.77 (3H,s), 3.90 (2H,dd,J=12,5 Hz), 3.99 (2H,dd,J=12,7 Hz), 6.76 (2H,m), 6.79 (1H,m); ir (Nujol): 3300 cm^{-1}; observed m/e: 212 (100%), 164 (79%), 149 (73%); exact mass for $C_{11}H_{16}O_4$ calculated 212.10484, observed 212.10464

2-(4-Carboxyphenyl)-1,3-dioxolane (73)

To a 500 ml round bottom flask equipped with a Dean-Stark water entrainment head and a magnetic stirrer was added 15.0 gm (0.1 mol) of 4-carboxybenzaldehyde (purchased from Aldrich and used as supplied), 150 ml of dry benzene, 5.6 ml (0.1 mol) of ethylene glycol and 52 mg (0.3 mmol) of p-toluenesulfonic acid. The reaction mixture was refluxed 8 hours. The benzene was removed on the rotary evaporator. The residue was added to 100 ml of 8% sodium hydroxide and warmed until homogeneous (ca. 1 hr). Once cooled to room temperature, the solution was neutralized with 12 ml of glacial acetic acid. The reaction mixture was extracted with chloroform (3 x 50 ml). The chloroform extracts were washed with water (2 x 50 ml), dried over anhydrous sodium sulfate and evaporated to dryness on the

rotary evaporator. Yield 10.3 gm (53%) of a white powder. The crude acetal was recrystallized twice from chloroform. Yield 6.8 gm (35%) of a white crystalline solid, mp = 179-180°C (literature mp = 177-178°C (34)). ^1H NMR ($CDCl_3$): 4.11 (4H,m), 5.89 (1H,s), 7.60 (2H,d,J=8 Hz), 8.14 (2H,d,J=8 Hz); ir (Nujol): 1685 cm^{-1}; observed m/e: 194 (40%), 193 (99%), 149 (100%); exact mass for $C_{10}H_{10}O_4$ calculated 194.05789, observed 194.05758

2-(4-Carboxyphenyl)-5,5-dimethyl-1,3-dioxane (74)

To a 500 ml round bottom flask equipped with a Dean-Stark water entrainment head and a magnetic stirrer was added 15.0 gm (0.1 mol) of 4-carboxybenzaldehyde (purchased from Aldrich and used as supplied), 150 ml of dry benzene, 10.4 gm (0.1 mol) of 2,2-dimethyl-1,3 propane diol and 52 mg (0.3 mmol) of p-toluene sulfonic acid. The reaction mixture was refluxed 24 hours. The benzene was removed on the rotary evaporator. The residue was added to 100 ml of 8% sodium hydroxide and warmed until homogeneous (ca. 1 hr). The solution was neutralized with 12 ml of glacial acetic acid. The precipitated acetal was collected by filtration, then dissolved in chloroform (200 ml). The chloroform solution was washed with water (50 ml), dried over anhydrous sodium sulfate and evaporated to dryness on the rotary evaporator. Yield 20.1 gm (85%) of a white crystalline solid. The crude acetal was recrystallized twice from chloroform. Yield 17.8 gm (75%) of a white crystalline solid, mp = 224-225°C. ^1H NMR ($CDCl_3$):

0.82 (3H,s), 1.30 (3H,s), 3.67 (2H,d,J=12 Hz), 3.80 (2H,d, J=12 Hz), 5.45 (1H,s), 7.62 (2H,d,J=8 Hz), 8.13 (2H,d,J=8 Hz); ir (Nujol): 1685 cm^{-1}; observed m/e: 236 (40%), 235 (43%), 191 (10%), 149 (86%), 56 (100%); exact mass for $C_{13}H_{16}O_4$ calculated 236.10485, observed 236.10426

2-(4-Diazoacetylphenyl)-5,5-dimethyl-1,3-dioxane (75)

To a 100 ml round bottom flask equipped with a reflux condenser and magnetic stirrer was added 8.7 gm (37 mmol) of 2-(4-carboxyphenyl)-5,5-dimethyl-1,3-dioxane 74 and 45 ml of thionyl chloride. The thionyl chloride had previously been distilled from triphenyl phosphite (ca. 15% v/v). The reaction mixture was refluxed until it was homogeneous (ca. 30 min). The reflux condenser was then replaced with a condenser set for distillation and the excess thionyl chloride was distilled out. Dry benzene (50 ml) was added and distilled out. This was repeated three times to ensure complete removal of traces of thionyl chloride. The acid chloride was then diluted with ether (50 ml) and slowly added to 1500 ml of ice cooled ethereal diazomethane (The diazomethane concentration of 0.08 M/l was determined by reacting 10 ml aliquots of the diazomethane solution with 0.5 gm samples of benzoic acid and titrating the excess benzoic acid with 0.1 N sodium hydroxide to a phenolphthalein endpoint). This solution was stirred 24 hours under a nitrogen atmosphere. The reaction mixture was then washed with aqueous sodium bicarbonate (100 ml), washed with water

(2 x 50 ml), and dried over anhydrous magnesium sulfate. The ether was removed on the rotary evaporator. Yield 8.9 gm (93%) of a yellow solid. The crude product was recrystallized twice from ether/n-pentane. Yield 3.6 gm (38%) of a yellow crystalline solid, mp = 109-110°C. ^{1}H NMR ($CDCl_3$): 0.80 (3H,s), 1.28 (3H,s), 3.63 (2H,d,J=12 Hz), 3.79 (2H,d,J=12 Hz), 5.42 (1H,s), 5.88 (1H,s), 7.58 (2H,d,J=8 Hz), 7.77 (2H,d, J=8 Hz); ir (Nujol): 1615 and 2110 cm^{-1}; UV (EtOH): 206 (4.14), 253 (4.17), 297 (4.16); observed m/e: 260 (100%), 219 (19%), 145 (72%), 102 (41%); exact mass for $C_{14}H_{16}N_2O_3$ calculated 260.11607, observed 260.11902

2-(4-(Carboethoxymethyl)-phenyl)-5,5-dimethyl-1,3-dioxane (76)

An ethanolic solution of 2-(4-diazoacetylphenyl)-5,5-dimethyl-1,3-dioxane **75** was prepared by dissolving 0.78 gm (3 mmol) in 85 ml of absolute ethanol. This solution was divided into 5 equal portions, placed in 11 mm i.d. Pyrex irradiation tubes and irradiated with a medium pressure mercury lamp. After 5 hours irradiation, the absorbance of the solution, measured in the irradiation tube at 400 nm, had dropped from an initial value of 1.76 to 0.57. The five solutions were combined and evaporated to dryness on the rotary evaporator. Yield 0.80 gm (96%) of a yellow oil. The ^{1}H NMR spectrum in $CDCl_3$ of the crude product showed the disappearance of the singlet at 5.9 ppm assigned to the diazo ketone group and the appearance of a new singlet at 3.6 ppm which integrated to two protons. The ^{1}H NMR spectrum also

showed a new triplet at 1.2 ppm, J=7 Hz, which integrated to 3 protons and a new quartet at 4.1 ppm, J=7 Hz, which integrated to 2 protons. IR of the crude product showed a strong peak at 1740 cm^{-1} and did not show the peak at 2110 cm^{-1} associated with the diazo ketone group. The crude product was not further purified, as this approach to the cyclobutane linked porphyrin benzoquinone had been determined to be unsuccessful using diethyl malonate as a odel for **76**.

Attempted synthesis of diethyl-3-(2,5-dimethoxyphenyl)-1,1-cyclobutanedicarboxylate (77). Formation of 2-(2,5-dimethoxyphenyl)-3-ethoxy-propene (78)

To a 25 ml, three necked pear flask equipped with a dropping funnel, a reflux condenser capped with a nitrogen inlet, a magnetic stirrer and a septum cap was added 1 ml of a sodium ethoxide solution (prepared by reacting 60 mg (2.6 mmol) of metallic sodium with 10 ml of absolute ethanol), 0.04 ml (0.26 mmol) of diethyl malonate and 5 ml of absolute ethanol. This solution was heated to reflux. A solution prepared by dissolving 135 mg (0.26 mmol) of 2-(2,5-dimethoxyphenyl)-1,3-propanediol ditosylate **66** in 5 ml of absolute ethanol and 5 ml of dry tetrahydrofuran was added, all at once, to the refluxing malonate solution. The reaction mixture was refluxed 8 hours then allowed to cool to room temperature. Water (50 ml) was added. This solution was extracted with ether (3 x 30 ml). The ether extracts were washed with water (30 ml), dried over anhydrous magnesium

sulfate, and evaporated to dryness on the rotary evaporator. Yield 38.4 mg (64%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$): 1.18 (3H,t,J=7 Hz), 3.52 (2H,q,J=7 Hz), 3.76 (6H,s), 4.32 (2H,m), 5.26 (1H,m), 5.43 (1H,m), 6.80 (3H,m)

The crude product was not further purified since the ^{1}H NMR indicated the product to be the undesired 2-(2,5-dimethoxyphenyl)-3-ethoxy-propene **78** instead of the desired diethyl-3-(2,5-dimethoxyphenyl)-1,1-cyclobutane-dicarboxylate **77**.

Diethyl 2-(2,5-dimethoxyphenyl)malonate (79)

To a 250 ml, three necked round bottom flask equipped with a dropping funnel and a fractionating column was added a solution of 22.4 gm (0.1 mol) of ethyl (2,5-dimethoxy phenyl)acetate **68** in 80 ml of diethyl carbonate. This solution was heated to reflux and a sodium ethoxide solution, prepared by reacting 2.3 gm (0.1 mol) of metallic sodium with 50 ml of absolute ethanol, was added dropwise. The ethanol was simultaneously distilled out. When the ethanol had been completely distilled out (ca. 1 hr.) the reaction mixture was cooled to room temperature then poured into 100 ml of ice-cold dilute hydrochloric acid (2N). This mixture was extracted with diethyl ether (3 x 50 ml). The ether extracts were washed with water (50 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator. Diethyl carbonate was removed by vacuum distillation,

bp = 35°C at 29 mm Hg. This yielded 26.0 gm (88%) of a yellowish oil. The crude product was used in subsequent reactions without further purification.

A small portion of the product was distilled, bp = 100 - 102°C at 0.8 mm Hg, to give a colourless oil (literature bp = 90-103°C at 7 mm Hg (57)). ^{1}H NMR ($CDCl_3$): 1.27 (6H,t, J=7 Hz), 3.76 (3H,s), 3.78 (3H,s), 4.23 (4H,q, J=7 Hz), 5.08 (1H,s), 6.82 (2H,m), 6.93 (1H,m); ir (film): 1755, 1735 cm^{-1} (literature ir (film): 1735 cm^{-1} (57)); observed m/e: 296 (44%), 224 (100%), 151 (80%); exact mass for $C_{15}H_{20}O_6$ calculated 296.12598, observed 296.12573

Diethyl 2-(2,5-dimethoxyphenyl)-2-methyl-malonate (80)

To a 250 ml three necked round bottom flask equipped with a dropping funnel, a reflux condenser and a magnetic stirrer was added 100 ml of absolute ethanol and 2.4 gm (105 mmol) of metallic sodium. When the sodium had all dissolved, the solution was ice cooled and to it was added dropwise a solution of 20.7 gm (70 mmol) of diethyl 2-(2,5-dimethoxy phenyl)malonate **79** in 100 ml of absolute ethanol. After 30 minutes, 6.6 ml (105 mmol) of methyl iodide was added dropwise. The reaction mixture was then refluxed for 30 minutes. The reaction mixture was cooled to room temperature and diluted with 200 ml of water. This mixture was extracted with diethyl ether (3 x 100 ml). The ether extracts were washed with water (50 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary

evaporator. Yield 20.1 gm (92%) of a very viscous yellow oil, which could not be distilled due to extensive decomposition occurring in the stillpot (literature reports purification by preparative thick layer chromatography (58)). That a transformation had been effected was proved by GLC analysis (2 m glass column, 5 mm id, 10% OV 101 on chromasorb W, 220°C isothermal, He flow 30 ml/min) of the product mixture and comparing it with the starting material. This showed clean conversion of >95% of the starting material, retention time equal 8.63 minutes, to a single product, retention time equal 9.56 minutes. The ^1H NMR spectrum in $CDCl_3$ of the crude product showed the disappearance of the singlet at 5.1 ppm assigned to the benzylic methine and the appearance of a new singlet at 1.8 ppm which integrated to 3 protons. The other signals in the ^1H NMR spectrum of this material agree with the partial NMR data given in the literature (58). This product was used in subsequent reactions without further purification.

2-(2,5-Dimethoxyphenyl)-2-methyl-1,3-propanediol (81)

To a 1000 ml three necked round bottom flask equipped with a dropping funnel, a reflux condenser capped with a nitrogen inlet and a magnetic stirrer was added 12.0 gm (316 mmol) of lithium aluminum hydride and 400 ml of dry ether. A solution of 19.6 gm (63 mmol) of diethyl 2-(2,5-dimethoxy phenyl)-2-methyl-malonate **80** in 150 ml of dry ether was slowly added. The rate of addition was controlled so as to maintain a gentle reflux. 30 minutes after the addition

was complete, ethyl acetate was added to destroy the excess lithium aluminum hydride. The solution was then cooled in an ice bath and 400 ml of 10% sulphuric acid was added. The reaction mixture was then extracted with ether (3 x 200 ml). The ether extracts were washed with water, dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary evaporator. Yield 13.6 gm (95%) of a yellow oily powder. The crude diol was recrystallized from ether/30-60 petroleum ether. Yield 7.5 gm (52%) of a white crystalline solid, mp = 98-99°C. ^{1}H NMR ($CDCl_3$): 1.29 (3H,s), 2.55 (2H,s(broad)), 3.77 (3H,s), 3.81 (3H,s), 3.85 (2H,d(broad), J=12 Hz), 4.17 (2H,d(broad),J=12 Hz), 6.76 (1H,dd,J=8,3 Hz), 6.85 (1H,d,J=8 Hz), 7.03 (1H,d,J=3 Hz); ir (Nujol): 3300 cm^{-1}; observed m/e: 226 (65%), 178 (66%), 163 (100%); exact mass for $C_{12}H_{18}O_4$ calculated 226.12050, observed 226.12008

2-(2,5-Dimethoxyphenyl)-2-methyl-1,3-propanediol ditosylate (82)

To a 250 ml round bottom flask equipped with a magnetic stirrer was added 5.0 gm (22.1 mmol) of 2-(2,5-dimethoxy phenyl)-2-methyl-1,3-propane-diol **81**, 12.6 gm (66.3 mmol) of p-toluenesulfonyl chloride (recrystallized from 30-60 petroleum ether), and 100 ml of dry pyridine. This mixture was stirred at room temperature until homogeneous (ca. 5 min). The reaction vessel was then sealed and stored in the refrigerator over night. The reaction mixture was poured onto crushed ice (100 gm) and extracted with ether (3 x 100 ml).

The ether extracts were washed with dilute hydrochloric acid (50 ml 2N), followed by water (2 x 50 ml), dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary evaporator. Yield 11.4 gm (96%) of a viscous yellow oil. The crude product was crystallized from ether/pentane yielding 9.0 gm (76%) of a white solid, mp = 91-92°C. ^{1}H NMR ($CDCl_3$): 1.34 (3H,s), 2.45 (6H,s), 3.47 (3H,s), 3.74 (3H,s), 4.30 (4H,s), 6.61 (1H,d,J=8 Hz), 6.66 (1H,d,J=3 Hz), 6.72 (1H,dd,J=8,3 Hz), 7.29 (4H,d,J=8 Hz), 7.64 (4H,d,J=8 Hz); ir (Nujol): 1375, 1175 cm^{-1}; observed m/e: 534 (5%), 348 (51%), 163 (100%), 91 (98%); exact mass for $C_{26}H_{30}O_8S_2$ calculated 534.13817, observed 534.13770

2,2-Dimethyl-1,3-propanediol ditosylate (83)

To a 250 ml round bottom flask equipped with a magnetic stirrer was added 2.5 gm (24 mmol) of 2,2-dimethyl-1,3-propane diol (purchased from Aldrich and used as supplied), 9.2 gm (48 mmol) of p-toluenesulfonyl chloride (recrystallized from 30-60 petroleum ether), and 100 ml of dry pyridine. This mixture was stirred until homogeneous (ca. 5 min). The reaction vessel was then sealed and stored in the refrigerator over night. The reaction mixture was poured onto crushed ice (100 gm) and extracted with chloroform (3 x 100 ml). The chloroform extracts were washed with dilute hydrochloric acid (50 ml 2N), followed by water (2 x 50 ml), dried over anhydrous sodium sulfate and evaporated to dryness on the rotary evaporator. Yield 9.9 gm (100%) of a viscous slightly

orange oil, which slowly crystallized. The crude product was recrystallized from chloroform/ether. Yield 8.9 gm (90%) of a white crystalline solid, mp = 121-122°C (literature mp = 122°C (59)). ^{1}H NMR ($CDCl_3$): 0.86 (6H,s), 2.44 (6H,s), 3.69 (4H,s), 7.33 (4H,d,J=8 Hz), 7.71 (4H,d,J=8 Hz); ir (Nujol): 1370, 1180 cm^{-1}; observed m/e: 412 (12%), 155 (100%), 91 (79%); exact mass for $C_{19}H_{24}O_6S_2$ calculated 412.10140, observed 412.10016

Diethyl 3,3-dimethyl-1,1-cyclobutanedicarboxylate (84)

To a 100 ml three necked round flask equipped with a reflux condenser capped with a nitrogen inlet, a mechanical stirrer, and a dropping funnel was added 0.16 gm (7.0 mmol) of metallic sodium and 20 ml of dry xylenes (freshly distilled from sodium). The mixture was heated to reflux with vigourous stirring. After 5 minutes reflux the heating bath was removed and the mixture was allowed to slowly cool to room temperature. A solution of 1.5 ml (9.9 mmol) of diethyl malonate in 5 ml of dry xylenes was added dropwise to the resulting suspension of sodium sand in xylenes. The mixture was reheated to reflux. The dropping funnel was briefly removed and 1.00 gm (2.4 mmol) of powdered 2,2-dimethyl-1,3-propane-ditosylate **83** was added as quickly as possible. The dropping funnel was replaced as soon as the powder had been added. After 12 hours reflux the reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with ether (100 ml), and poured onto ice (50 gm). The ether

layer was isolated, washed with dilute hydrochloric acid (25 ml 2 N), followed by water (2 x 50 ml), dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary evaporator. Yield 1.0 gm of a brownish oil and a white solid. The solid was isolated and identified as unreacted 2,2-dimethyl-1,3-propane-ditosylate **83**, yield 0.40 gm. The brownish oil, 0.60 gm, was chromatographed on a 50 gm silica column, 10% ether in 30-60 petroleum ether as eluent. The first fraction off the column was isolated. Yield 0.14 gm (25%) of a colourless oil, bp = 126°C (literature bp = 118-119 at 20 mm Hg (60)). ^{1}H NMR ($CDCl_3$): 1.09 (6H,s), 1.22 (6H,t, J=7 Hz), 2.35 (4H,s), 4.17 (4H,q,J=7 Hz); ir (film): 1730, 1750 cm^{-1}; observed m/e (chemical ionization): 229 (100%), 183 (78%), 155 (34%); exact mass for $C_{12}H_{21}O_4$ (parent ion + H^+) calculated 229.14397, observed 229.14427

Attempted synthesis of diethyl-3-(2,5-dimethoxyphenyl)-3-methyl-1,1-cyclobutanedicarboxylate (85). Formation of 5-methoxy-3-methyl-3-(p-tolylsulfonylmethyl)coumaran (86)

A solution of diethyl sodio-malonate was prepared by dissolving 0.3 gm (13 mmol) of metallic sodium in 20 ml of absolute ethanol, containing 2.0 ml (13 mmol) of diethyl malonate. This solution was diluted to 25 ml with absolute ethanol. 0.5 ml (0.26 mmol) of this solution was transferred to a Carius tube and evaporated to dryness using a high vacuum pump. A solution of 50 mg (0.09 mmol) of 2-(2,5-dimethoxyphenyl)-2-methyl-1,3-propanediol ditosylate **82**

dissolved in 2.0 ml of xylenes, previously stored over sodium wire, was added to the dry powder residue in the Carius tube. The atmosphere within the Carius tube was replaced with dry nitrogen, by flushing the tube for ca. 10 minutes. The tube was then connected to a nitrogen line and heated to reflux for 2 hours. The reaction mixture was allowed to cool to room temperature. Ether (50 ml) was added. The reaction mixture was washed with dilute hydrochloric acid (20 ml 0.1 N), then water (2 x 30 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator. Yield 34.9 mg (107%) of a yellow oil. The crude product was purified by preparative thick layer chromatography on silica, 10% ether in hexanes as eluent. The major band isolated, 15.8 mg (48%), is a pale yellow oil. ^{1}H NMR ($CDCl_3$): 1.39 (3H,s), 2.44 (3H,s), 3.73 (3H,s), 3.94 (2H,s(broad)), 4.08 (1H,d,J=10 Hz), 4.41 (1H,d,J=10 Hz), 6.57 (1H,m), 6.68 (2H,m), 7.31 (2H,d, J=8 Hz), 7.72 (2H,d,J=8 Hz); observed m/e: 348 (21%), 163 (100%), 49 (80%); exact mass for $C_{18}H_{20}O_5S$ calculated 348.10312, observed 348.10320

The spectral data indicate the product is the undesired 5-methoxy-3-methyl-3-(p-tolylsulfonylmethyl)-coumaran **86** instead of the desired diethyl-3-(2,5-dimethoxyphenyl)-3-methyl-1,1-cyclobutanedicarboxylate **85**.

2,5-Dimethoxystyrene (87)

To a 250 ml three neck round bottom flask equipped for vacuum distillation, with a dropping funnel, and a magnetic

stirrer was added 2.0 gm (15 mmol) of fused potassium bisulfate and 0.02 gm (0.1 mmol) of 2,6-di-t-butyl-p-cresol. A mixture of 18.2 gm (100 mmol) of 1,4-dimethoxy-2-(1-hydroxyethyl)benzene **90** and 0.02 gm (0.1 mmol) of 2,6-di-t-butyl-p-cresol were placed in the dropping funnel and the system was evacuated to a pressure of 20 mm Hg. The reaction pot was placed in a preheated oil bath set at 190°C and the 1,4-dimethoxy-2-(1-hydroxyethyl)benzene was slowly added to the potassium bisulfate. The product was distilled from the reaction pot as it formed, bp = 132°C at 20 mm Hg. The crude product was dissolved in ether (100 ml), washed with aqueous sodium bicarbonate (25 ml 10 %), washed with water (3 x 50 ml), and dried over anhydrous magnesium sulfate. The ether was removed on the rotary evaporator. Yield 11.1 gm (68%) of a colourless oil. Any attempt to redistill this product resulted in polymerization (literature bp = 61°C at 0.05 mm Hg with polymerization in the stillpot (41)).

A small portion of the product was purified sufficiently for characterization by chromatography on silica gel using 10% ether in 30/60 petroleum ether as eluent. ^{1}H NMR ($CDCl_3$): 3.78 (3H,s), 3.79 (3H,s), 5.27 (1H,dd,J=10,2 Hz), 5.72 (1H,dd,J=18,2 Hz), 6.78 (2H,m), 7.03 (1H,dd,J=18,10 Hz), 7.05 (1H,m) (literature ^{1}H NMR: 3.8 (6H,2s), 5.2-5.35 (1H,dd), 5.5-5.9 (1H,dd), 6.8-7.3 (4H,m) (41)); observed m/e: 164 (100%), 149 (53%), 121 (46%); exact mass for $C_{10}H_{12}O_2$ calculated 164.08372, observed 164.08346

To a 250 ml three neck round bottom flask equipped with a dropping funnel, reflux condenser, and magnetic stirrer was added 0.5 gm (13 mmol) of lithium aluminum hydride and 50 ml of dry ether. A solution of 9.5 gm (58 mmol) of the impure 2,5-dimethoxystyrene **87** in 100 ml of dry ether was added dropwise to the lithium aluminum hydride. 30 minutes after the addition was complete, wet ether (ca. 200 ml) then water (ca. 25 ml) was added to quench the excess lithium aluminum hydride. The ether was decanted from the aluminum salts and the salts were rinsed with fresh ether (2 x 100 ml). The combined ether phases were washed with water (3 x 50 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator. Yield 9.3 gm (98%) of a colourless oil, which was used in subsequent reactions without further purification.

2-(4-Bromophenyl)-1,3-dioxolane (88)

To a 250 ml round bottom flask equipped with a Dean-Stark water entrainment head and a magnetic stirrer was added 11 gm (59 mmol) of 4-bromobenzaldehyde (purchased from Aldrich and used as supplied), 17 ml (305 mmol) of ethylene glycol, 0.1 gm (0.6 mmol) of p-toluenesulfonic acid and 100 ml of dry benzene. The reaction mixture was refluxed 8 hours. The reaction mixture was diluted with 200 ml of ether, washed with saturated sodium bicarbonate solution (50 ml) and washed with water (2 x 100 ml). The ether layer was dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary

evaporator. Yield 10.9 gm (78%) of a clear colourless oil, after distillation, bp = 121-124 at . mm Hg (literature bp = 107 at 2 mm Hg (61)). The product slowly crystallized, mp = 32-33°C (literature mp = 33°C (61)). ^{1}H NMR ($CDCl_3$): 4.06 (4H,m), 5.77 (1H,s), 7.36 (2H,d,J=8 Hz), 7.51 (2H,d,J=8 Hz); ir (Nujol): 1040, 1090 cm^{-1}; observed m/e: 230 (15%), 229 (63%), 228 (15%), 227 (63%), 185 (98%), 183 (100%); exact mass for $C_9H_9O_2Br$ calculated 227.97855, observed 227.97861

2,2-Dichloro-3-(2,5-dimethoxyphenyl)cyclobutanone (89)

To a 500 ml three neck round bottom flask equipped with two dropping funnels, a reflux condenser capped with a nitrogen inlet, and a magnetic stirrer was added 8.2 gm (50 mmol) of 2,5-dimethoxystyrene **87** and 100 ml of hexanes. A solution of 7.0 gm (48 mmol) of dichloroacetyl chloride (prepared by treating dichloroacetic acid with thionyl chloride in the presence of a catalytic amount of dimethyl formamide) in 50 ml of hexanes was added to the 2,5-dimethoxy styrene solution. The reaction mixture was heated to reflux. A solution of 6.9 ml (50 mmol) of triethylamine in 100 ml of hexanes was added dropwise to the reaction mixture. After 8 hours the reaction was quenched by the addition of wet ether (ca. 200 ml). The reaction mixture was washed with water (3 x 100 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator. Yield 15.2 gm of a yellow oil. GLC analysis (30 meter DB1 Megabore column, 150°C isothermal, He flow 30 ml/min) of this material

indicated it was ca. 15% pure, the major contaminant being unreacted 2,5-dimethoxystyrene.

The crude product was chromatographed on a 150 gm silica column using 5% ether in hexanes as eluent. Yield 1.7 gm (12.4% based on starting styrene) of a yellow crystalline solid. The mother liquor from this crystallization contained an additional 3.6 gm (26.3% based on starting styrene) of a yellow oil which GLC analysis indicated was also 2,2-dichloro-3-(2,5-dimethoxyphenyl)-cyclobutanone. However, this material could not be induced to crystallize. The crystalline material was recrystallized from ether/pentane to give a pale yellow solid, mp = 68-69°C. ^{1}H NMR ($CDCl_3$): 3.61 (2H,d(broad), J=9 Hz), 3.79 (3H,s), 3.80 (3H,s), 4.29 (1H,t(broad),J=9 Hz), 6.74 (1H,m), 6.86 (2H,m); ir (Nujol): 1810 cm^{-1}; observed m/e: 276 (14%), 274 (21%), 234 (64%), 232 (100%); exact mass for $C_{12}H_{12}Cl_2O_3$ calculated 274.01633, observed 274.01632

1,4-Dimethoxy-2-(1-hydroxyethyl)benzene (90)

To a 500 ml three neck round bottom flask equipped with a dropping funnel, a reflux condenser capped with a nitrogen inlet, and a magnetic stirrer was added 8.6 gm (0.35 mol) of magnesium turnings and 100 ml of dry ether. A solution of 22 ml (0.35 mol) of methyl iodide in 100 ml of dry ether was slowly added to the magnesium turnings; formation of the Grignard reagent was spontaneous. The rate of addition was adjusted to maintain a gentle reflux. The reaction mixture was stirred at room temperature for about 30 minutes after the

reflux had subsided, then cooled in an ice bath. A solution of 19.3 gm (0.116 mol) of 2,5-dimethoxybenzaldehyde in 100 ml of dry ether was added dropwise, with rapid stirring to the cold Grignard solution. The reaction mixture turned a pale yellow colour and became very cloudy upon the addition of the 2,5-dimethoxybenzaldehyde. The reaction mixture was stirred in the ice bath for 30 minutes following completion of the addition, then poured into 200 ml of ice cold, saturated aqueous ammonium chloride. This mixture was extracted with ether (3 x 100 ml). The ether extracts were washed with dilute hydrochloric acid (50 ml 0.1 N), with water (2 x 100 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator. Yield 19.3 gm (91%) of a pale yellow oil.

A sample of the crude product was purified by vacuum distillation for characterization, bp = 125-127°C at 0.3 mm Hg (literature bp = 118°C at 2 mm Hg (41)), to give a colourless oil. ^{1}H NMR ($CDCl_3$): 1.49 (3H,d,J=6 Hz), 2.71 (1H,d(broad), J=4 Hz), 3.78 (3H,s), 3.82 (3H,s), 5.06 (1H,m), 6.75 (1H,dd, J=8,3 Hz), 6.81 (1H,d,J=8 Hz), 6.94 (1H,d,J=3 Hz) (literature ^{1}H NMR: 1.33-1.46 (3H,d), 3.3 (1H,broad), 3.7 (6H,2s), 4.9-5.2 (1H,q), 6.7-7.0 (3H,m) (41)); ir (film): 3400 cm^{-1}; observed m/e: 182 (68%), 167 (87%), 139 (100%); exact mass for $C_{10}H_{14}O_3$ calculated 182.09428, observed 182.09476

2-(4-Bromophenyl)-5,5-dimethyl-1,3-dioxane (92)

To a 250 ml round bottom flask equipped with a Dean-Stark water entrainment head and a magnetic stirrer was added 4.4 gm (24 mmol) of 4-bromobenzaldehyde (purchased from Aldrich and used as supplied), 2.6 gm (25 mmol) of 2,2-dimethyl-1,3-propane diol, 0.1 gm (0.6 mmol) of p-toluenesulfonic acid and 80 ml of dry benzene. The reaction mixture was refluxed 8 hours. The reaction mixture was diluted with 200 ml of ether, washed with saturated sodium bicarbonate solution (50 ml) and washed with water (2 x 100 ml). The ether layer was dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary evaporator. Yield 6.2 gm (96%) of a yellowish oil, which slowly crystallized. The crude product was recrystallized from methanol/water, mp = 61-62°C. ^{1}H NMR ($CDCl_3$): 0.79 (3H,s), 1.27 (3H,s), 3.63 (2H,d,J=11 Hz), 3.76 (2H,d,J=11 Hz), 5.34 (1H,s), 7.37 (2H,d,J=8 Hz), 7.50 (2H,d, J=8 Hz); ir (Nujol): 1020, 1100 cm^{-1}; observed m/e: 272 (52%), 271 (60%), 270 (53%), 269 (58%), 187 (49%), 185 (100%), 183 (52%); exact mass for $C_{12}H_{15}O_2Br$ calculated 270.02550, observed 270.02623

2-(4-(1-Hydroxy-1-methylbutyl)phenyl)-5,5-dimethyl-1,3-dioxane (93)

To a 25 ml three neck pear flask equipped with reflux condenser capped with a nitrogen inlet, a dropping funnel, a septum cap and a magnetic stirrer was added 100 mg (0.4 mmol) of 2-(4-bromophenyl)-5,5-dimethyl-1,3-dioxane **92** and 10 ml of

dry tetrahydrofuran. The reaction vessel was cooled in a dry ice/acetone bath. 0.65 ml (1.1 mmol) of t-butyl lithium (1.7M in pentane) was added to the reaction mixture. A solution of 0.04 ml (0.4 mmol) of 2-pentanone in 2 ml of dry tetrahydrofuran was added dropwise to the aryl lithium solution. 15 minutes later, the reaction mixture was removed from the bath and warmed to room temperature. The reaction mixture was diluted with ether (50 ml) and washed with water (2 x 30 ml). The ether layer was dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary evaporator. Yield 76 mg (74%) of a yellow oil. GLC analysis (15 m Mega Bore DB1 column, 150°C isothermal, He flow 30 ml/min) indicated the product mixture consisted mainly of one product (>80%). GC-MS (chemical ionization) of the product mixture indicated the major product had a molecular weight of 278. This corresponds to the desired product. The observed fragments of the major product are m/e: 279 (67%), 261 (100%), 235 (96%). ^{1}H NMR ($CDCl_3$): 0.79 (3H,s), 0.82 (3H,t), 1.17 (2H,m), 1.30 (3H,s), 1.50 (3H,s), 1.74 (2H,t), 3.64 (2H,d), 3.77 (2H,d), 5.39 (1H,s), 7.42 (4H,m). The ^{1}H NMR spectrum of the crude product also contained several small peaks barely above the base line. These peaks are attributed to the other unidentified components of the product mixture. Since the product of this reaction was of no value, except to indicate that the reaction had proceeded as planned, and since this reaction yielded one major product consistent with the reaction proceeding as planned, the product was not further purified.

Attempted synthesis of 2,2-dichloro-3-(2,5-dimethoxyphenyl)-1-methyl-cyclobutanol (94), formation of 5,5-dichloro-4-(2,5-dimethoxyphenyl)-2-methyl-2-pentanol (95)

To a 25 ml three neck pear flask equipped with a reflux condenser capped with a nitrogen inlet, a septum cap, a stopper, and a magnetic stirrer was added 50 mg (0.18 mmol) of 2,2-dichloro-3-(2,5-dimethoxyphenyl)cyclobutanone **89** and 10 ml of dry tetrahydrofuran. The reaction mixture was cooled in a dry ice/acetone bath. 0.12 ml (0.18 mmol) of methyl lithium (1.5M in ether) was added to the cyclobutanone solution. After 15 minutes stirring, the reaction mixture was removed from the bath and allowed to warm to room temperature. Wet ether (25 ml) was added. The ether layer was isolated, washed with water (2 x 20 ml), dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary evaporator. Yield 43 mg (81%) of a yellow oil. GLC analysis (15 m Mega Bore DB1 column, 150°C isothermal, He flow 30 ml/min) indicated several products and a large amount of unchanged cyclobutanone. This was confirmed by GC-MS analysis of the product mixture, which also revealed that the major product had a molecular weight of 306. This corresponds to the addition of two equivalents of methyl lithium. The observed major fragments of this compound were m/e: 306 (50%), 270 (69%), 181 (100%). ^{1}H NMR analysis of this mixture was uninformative, as was infra-red analysis. The product mixture was not separated or further analyzed, as the presence of large amounts of starting material and of the product derived

from double addition of methyl lithium indicate that it is necessary to dechlorinate the cyclobutanone before the addition of the phenyl lithium.

3-(2,5-Dimethoxyphenyl)cyclobutanone (96)

To a 250 ml three neck round bottom flask equipped with a reflux condenser, a dropping funnel, a stopper, and a magnetic stirrer was added 0.95 gm (14.6 mmol) of zinc powder and 1.01 gm (19.1 mmol) of powdered ammonium chloride. The reaction vessel was placed in an oil bath set at 100°C. A solution of 1.24 gm (4.5 mmol) of 2,2-dichloro-3-(2,5-dimethoxyphenyl)cyclobutanone **89** in 125 ml of methanol was added, all at once, to the reaction flask. After 60 minutes reflux the reaction mixture was removed from the bath, allowed to cool (ca. 5 min), and diluted with water (200 ml). The reaction mixture was extracted with ether (3 x 100 ml). The combined ether extracts were washed with water (50 ml), dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary evaporator. Yield 0.89 gm (95%) of a colourless oil. GLC analysis (15 m Mega Bore DB1 column, 150°C isothermal, He flow 30 ml/min) indicated the product was >99% pure. The crude product was therefore not further purified. ^{1}H NMR ($CDCl_3$): 3.27 (4H,m), 3.64 (1H,q,J=8 Hz), 3.72 (3H,s), 3.73 (3H,s), 6.74 (3H,m); ^{13}C NMR ($CDCl_3$): 25.2 (CH), 52.8 (CH_2), 55.37 (CH_3), 55.43 (CH_3), 111.0, 111.1, 114.4 (aromatic CH), 132.1, 151.6, 153.2 (aromatic C), 207.8 (carbonyl C); ir (film): 1785 cm^{-1}; observed m/e: 206 (47%), 164 (100%), 149

(38%); exact mass for $C_{12}H_{14}O_3$ calculated 206.09428, observed 206.09383

3-(2,5-Dimethoxyphenyl)-1-(4-(4,4-dimethyl-2,6-dioxanyl) phenyl)cyclobutanol (97)

To a 500 ml three necked round bottom flask equipped with a reflux condenser capped with a nitrogen inlet, a dropping funnel, a septum cap and a magnetic stirrer was added 1.5 gm (5.6 mmol) of 2-(4-bromophenyl)-5,5-dimethyl-1,3-dioxane **92** and 150 ml of dry tetrahydrofuran. The reaction vessel was cooled in a dry ice/acetone bath. 7.8 ml (11.3 mmol) of t-butyl lithium (1.45M in pentane - this concentration was determined by titrating the t-butyl lithium using the method of Gall and House (62)) was added to the reaction mixture. 30 minutes later, a solution of 1.15 gm (5.6 mmol) of 3-(2,5-dimethoxyphenyl)cyclobutanone **96** in 100 ml of dry tetrahydrofuran was added dropwise to the aryl lithium solution. The reaction mixture was stirred at -78°C for 60 minutes after which time the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction was quenched by the addition of wet ether (100 ml). The reaction mixture was washed with water (2 x 100 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator. Yield 2.30 gm (103%) of a yellow oil. The crude product was purified by chromatography on a 100 gm silica column, 1:1 ether:hexanes

as eluent. Yield 1.33 gm (60%) of a very viscous yellowish oil, which very slowly crystallized.

A sample of the crude product was recrystallized from ether/hexanes to give a white crystalline solid, mp = 105 - 107°C. ^{1}H NMR ($CDCl_3$): 0.79 (3H,s), 1.29 (3H,s), 2.1 (1H,s (broad)), 2.47 (2H,ddt,J=12,10,3 Hz), 2.96 (2H,ddq, J=9,8,3 Hz), 3.21 (1H,tt,J=11,8 Hz), 3.65 (2H,d, J=12 Hz), 3.71 (3H,s), 3.77 (2H,d,J=12 Hz), 3.77 (3H,s), 5.41 (1H,s), 6.67 (1H,dd,J=10,3 Hz), 6.73 (1H,d,J=10 Hz), 6.86 (1H,d, J=3 Hz), 7.55 (2H,d,J=8 Hz), 7.64 (2H,d,J=8 Hz); ^{13}C NMR ($CDCl_3$): 21.9 (CH_3), 23.1 (CH_3), 25.1 (CH), 30.3 (C), 43.6 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 72.7 (C), 77.7 (CH_2), 101.5 (CH), 110.8, 111.1, 113.8, 125.6, 126.4 (aromatic CH), 134.0, 137.8, 146.2, 151.8, 153.7 (aromatic C); ir (Nujol): 3460 (sharp) cm^{-1}; observed m/e: 398 (10%), 312 (1%), 233 (1%), 164 (100%), 149 (16%); exact mass for $C_{24}H_{30}O_5$ calculated 398.20930, observed 398.20993

O-Benzyl-S-methyl-xanthate (98)

To a tared 50 ml three necked pear flask equipped with a magnetic stirrer was added ca. 400 mg of potassium hydride suspended in mineral oil. The mineral oil was removed by repeated washing with dry benzene. Evaporation of the final benzene wash under vacuum yielded 203 mg (5.1 mmol) of powdered potassium hydride. This flask was equipped with a dropping funnel and a reflux condenser capped with a nitrogen inlet. 1.0 ml of dry tetrahydrofuran was added, followed by

1.0 ml (0.38 mmol) of a solution prepared by dissolving 1.0 ml (9.6 mmol) of benzyl alcohol in 25 ml of dry tetrahydrofuran. 30 minutes later, 0.5 ml (0.83 mmol) of a solution prepared by dissolving 1.0 ml (16.6 mmol) of carbon disulfide in 10 ml of dry tetrahydrofuran was added, resulting in a bright yellow colour. 45 minutes later, 0.5 ml (0.64 mmol) of a solution prepared by dissolving 2.0 ml (32.1 mmol) of methyl iodide in 25 ml of dry tetrahydrofuran was added. The yellow colour slowly faded after the methyl iodide addition, leaving a milky suspension. The reaction mixture was stirred at room temperature for an additional 30 minutes, then added to a solution of 1 ml of glacial acetic acid in 5 ml of tetrahydrofuran. The reaction mixture was diluted with ether (25 ml), washed with saturated sodium bicarbonate solution (3 x 50 ml) and washed with water (2 x 50 ml). The ether layer was dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary evaporator. Yield 43.5 mg (56%) of a yellow oil. GLC analysis (15 m Mega Bore DB1 column, 50°C isothermal for 5 min then heated at 20°C/min to 250°C and held at 250°C for 10 min, He flow 30 ml/min) indicates the product is ca. 80% pure. ^{1}H NMR ($CDCl_3$): 2.57 (3H,s), 5.63 (2H,s), 7.40 (5H,s)

Toluene from O-benzyl-S-methyl-xanthate (98)

To a 25 ml pear flask equipped with a reflux condenser and a magnetic stirrer was added 23.2 mg (0.12 mmol) of the crude O-benzyl-S-methyl-xanthate **98** and 52.8 mg (0.18 mmol)

of tributyltin hydride (prepared by reducing a glyme solution of tributyltin chloride with sodium borohydride and collecting the fraction boiling at 94-95°C at 1.5 mm Hg (literature bp = 80°C at 0.4 mm Hg (63))). This mixture was dissolved in 10 ml of dry benzene and a crystal of 2,2'-azobisisobutyronitrile was added. The reaction mixture was heated to reflux. The progress of the reaction was followed by GLC (same conditions as used above). The reaction was complete in less than 1 hour. GLC analysis of the reaction mixture revealed no starting material, and the presence of toluene. The identity of the product as toluene was confirmed by co-injection with an authentic sample.

3-(2,5-Dimethoxyphenyl)-1-(4-(4,4-dimethyl-2,6-dioxanyl) phenyl)cyclobutene (100) and O-(3-(2,5-dimethoxyphenyl)-1-(4-(4,4-dimethyl-2,6-dioxanyl)phenyl)cyclobutyl)-S-methyl-xanthate (99)

To a tared 50 ml three necked pear flask equipped with a magnetic stirrer was added ca. 250 mg of potassium hydride suspended in mineral oil. The mineral oil was removed by repeated washing with dry benzene. Evaporation of the final benzene wash under vacuum yielded 84 mg (2.1 mmol) of powdered potassium hydride. The flask was equipped with a dropping funnel, a reflux condenser capped with a nitrogen inlet, and a septum cap. 5 ml of dry ether was added, followed by a solution of 99 mg (0.25 mmol) of 3-(2,5-dimethoxyphenyl)-1-(4-(4,4-dimethyl-2,6-dioxanyl)phenyl)cyclobutanol **97** in 5 ml

of dry ether. After 30 minutes, 0.17 ml (2.8 mmol) of carbon disulfide was added, by syringe, to the reaction mixture. The reaction mixture turned a bright yellow colour. After 30 minutes, 0.18 ml (2.9 mmol) of methyl iodide was added, again by syringe, to the reaction mixture. The yellow colour slowly faded, leaving a milky suspension. After 30 minutes, the reaction mixture was poured into a solution of 0.3 ml of glacial acetic acid in 50 ml of ether. This mixture was washed with saturated sodium bicarbonate solution (25 ml), water (3 x 50 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator. Yield 104.7 mg of a yellow oil.

The crude product was purified by preparative thick layer chromatography on silica, 10% ether in hexanes as eluent. Three bands were isolated, the band with the largest rf contained the most mass, 59.6 mg. The band with the second largest rf contained 12.5 mg. The band with the smallest rf, which by TLC analysis appears to be starting material, contained 16.7 mg (17%). The identity of this band as starting material was confirmed by mixed melting point.

The major product, 3-(2,5-dimethoxyphenyl)-1-(4-(4,4-dimethyl-2,6-dioxanyl)phenyl)cyclobutene **100**, was recrystallized from ether/hexanes, mp = 122-123°C. ^{1}H NMR ($CDCl_3$): 0.78 (3H,s), 1.28 (3H,s), 2.56 (1H,dd,J=12,2 Hz), 3.30 (1H,dd,J=12,4 Hz), 3.62 (2H,d,J=12 Hz), 3.73 (3H,s), 3.77 (2H,d,J=12 Hz), 3.80 (3H,s), 4.25 (1H,m), 5.37 (1H,s), 6.53 (1H,d,J=2 Hz), 6.69 (1H,dd,J=10,3 Hz), 6.77 (1H,d,J=10 Hz),

6.84 (1H,d,J=3 Hz), 7.38 (2H,d,J=8 Hz), 7.46 (2H,d,J=8 Hz); ^{13}C NMR ($CDCl_3$): 21.7 (CH_3), 22.8 (CH_3), 30.0 (C), 37.0 (CH), 37.4 (CH_2), 55.5 (CH_3), 55.9 (CH_3), 77.4 (CH_2), 101.3 (CH), 110.8, 111.0, 113.5, 124.3, 125.9 (aromatic CH), 128.5 (CH), 133.2, 134.9, 137.7, 145.9, 151.4, 153.4 (aromatic and olefinic C); observed m/e: 380 (28%), 349 (34%), 115 (33%), 69 (100%), 56 (51%); exact mass for $C_{24}H_{28}O_4$ calculated 380.19874, observed 380.19951

The minor product, O-(3-(2,5-dimethoxyphenyl)-1-(4-(4,4-dimethyl-2,6-dioxanyl)phenyl)cyclobutyl)-S-methyl-xanthate **99**, was recrystallized from hexanes, mp = 121-122°C. ^1H NMR ($CDCl_3$): 0.79 (3H,s), 1.29 (3H,s), 2.25 (3H,s), 2.86 (2H,ddt, J=12,10,3 Hz), 3.23 (2H,ddq,J=10,8,3 Hz), 3.58 (1H,tt, J=9,7 Hz), 3.67 (3H,s), 3.71 (2H,d,J=11 Hz), 3.78 (3H,s), 3.79 (2H,d,J=11 Hz), 5.40 (1H,s), 6.68 (2H,m), 6.85 (1H,d,J=2 Hz), 7.51 (2H,d,J=8 Hz), 7.65 (2H,d,J=8 Hz); ^{13}C NMR ($CDCl_3$): 12.7 (CH_3), 21.9 (CH_3), 23.1 (CH_3), 30.3 (C), 31.5 (CH), 42.6 (CH_2), 51.4 (CH), 55.8 (CH_3), 55.8 (CH_3), 77.7 (CH_2), 101.6 (CH), 111.0, 111.1, 113.6, 126.0, 127.5 (aromatic CH), 133.0, 137.1, 144.9, 151.5, 153.6 (aromatic C), 188.1 (thiocarbonyl); ir (Nujol): 1220, 1110 cm^{-1}; observed m/e: 488 (23%), 295 (40%), 164 (100%), 115 (66%), 69 (59%); exact mass for $C_{26}H_{32}O_5S_2$ calculated 488.16909, observed 488.16880

2-Phenyl-2-propanol (101)

To a 100 ml three necked round bottom flask equipped with a dropping funnel, a reflux condenser capped with a nitrogen

inlet, and a magnetic stirrer was added 0.5 gm (20 mmol) of magnesium turnings and 10 ml of dry ether. A solution of 1.1 ml (18 mmol) of methyl iodide dissolved in 10 ml of dry ether was slowly added to the magnesium turnings; formation of the Grignard reagent was spontaneous. The rate of addition was adjusted to maintain a gentle reflux. The reaction mixture was stirred at room temperature for 30 minutes after the reflux had subsided, then cooled in an ice bath. A solution of 1.7 ml (15 mmol) of acetophenone dissolved in 10 ml of dry ether was added dropwise, with rapid stirring to the cold Grignard solution. The reaction mixture turned a milky white with the addition of the acetophenone. The reaction mixture was stirred for 30 minutes at room temperature after the addition was complete. 30 ml of wet ether was added to quench the reaction. The ether layer was washed with water (3 x 50 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator. Yield 1.76 gm (89%) of a yellowish oil. GLC analysis (15 m Mega Bore DB1 column, 50°C isothermal for 5 min then heated at 20°C/min to 250°C and held at 250°C for 10 min , He flow 30 ml/min) indicates the product to be 68% pure. Chromatography on a 50 gm silica column, using 5% ether in hexanes as eluent, gave a fraction 93% pure by GLC analysis. ^{1}H NMR ($CHCl_3$): 1.57 (6H,s), 2.03 (1H,s(broad)), 7.37 (5H,m)

Attempted synthesis of O-(1-methyl-1-phenyl)ethyl-S-methyl-xanthate (102)

To a tared 50 ml three necked pear flask equipped with a magnetic stirrer was added ca. 400 mg of potassium hydride suspended in mineral oil. The mineral oil was removed by repeated washing with dry ben . Evaporation of the final benzene wash under vacuum yielded 216 mg (5.4 mmol) of powdered potassium hydride. The flask was equipped with a dropping funnel, a reflux condenser capped with a nitrogen inlet, and a septum cap. 5 ml of dry ether was added, followed by a solution of 34 mg (0.25 mmol) of 2-phenyl-2-propanol **101** in 5 ml of dry ether. After 30 minutes, 0.17 ml (2.8 mmol) of carbon disulfide was added, by syringe, to the reaction mixture. The reaction mixture turned a bright yellow colour. After 30 minutes, 0.18 ml (2.9 mmol) of methyl iodide was added, again by syringe, to the reaction mixture. The yellow colour slowly faded, leaving a milky suspension. After 30 minutes, the reaction mixture was poured into a solution of 0.6 ml of glacial acetic acid in 50 ml of ether. This mixture was washed with saturated sodium bicarbonate solution (25 ml), water (3 x 50 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness on the rotary evaporator. Yield 15.3 mg of a yellow oil. GLC analysis (same conditions as above) revealed the product to be 64% α-methyl styrene **103** and 30% starting material.

The products were identified by comparison with the product mixture from a previous larger scale reaction. The

product mixture from this previous reaction, which had been analyzed by GLC and GC-MS, contained 5 major components. The component with the shortest retention time had a molecular ion of 118 and a major fragment of 103, this is consistent with assigning it as α-methyl styrene **103**. The component with the next shortest retention time had a molecular ion of 136 and a retention time identical to that of starting material **101**, this was assigned as starting material. The component with the next shortest retention time had a molecular ion of 138 with a m+2 peak 14% as intense (64) and a major fragment of 91 with a m+2 peak 9% as intense, this is consistent with assigning it as dimethyl trithiocarbonate **105**. The component with the next shortest retention time had a molecular ion of 166 and a major fragment of 119, this is consistent with assigning it as the thio ether **104**. The major component with the longest retention time had a molecular ion of 226 and a major fragment of 119, this is consistent with assigning it as the xanthate **102**.

Attempted preparation of both cis (106) and trans (107) 1-(2,5-dimethoxyphenyl)-3-(4-(4,4-dimethyl-2,6-dioxanyl) phenyl)cyclobutane from O-(3-(2,5-dimethoxyphenyl)-1-(4-(4,4-dimethyl-2,6-dioxanyl)phenyl)cyclobutyl)-S-methyl-xanthate (99)

To a 25 ml pear flask equipped with a reflux condenser capped with a nitrogen inlet and a magnetic stirrer was added 27.9 mg (0.057 mmol) of O-(3-(2,5-dimethoxyphenyl)-1-(4-(4,4-

dimethyl-2,6-dioxanyl)phenyl)cyclobutyl)-S-methyl-xanthate **99** and 0.03 ml (0.112 mmol) of tributyltin hydride. This mixture was dissolved in 5 ml of toluene and a crystal of 2,2'-azobisisobutyronitrile was added. The reaction mixture was heated to reflux. After 1 hour, the product was isolated by evaporating the toluene under a stream of nitrogen. The very polar and very non-polar impurities were removed by preparative thick layer chromatography on silica, 10% ether in hexanes as eluent. Yield 11.2 mg of a colourless oil. ^{1}H NMR analysis of this material indicated that it was a complex mixture and that none of the starting xanthate remained. TLC analysis revealed this mixture consisted of two major and several minor components. The separation of these components was so poor and the yield so low that purification was impracticable. The major product was, however, identified as the cis isomer **106**, by TLC comparison with the product obtained from hydrogenation of 3-(2,5-dimethoxyphenyl)-1-(4-(4,4-dimethyl-2,6-dioxanyl)phenyl)cyclobutene **100**.

cis 1-(2,5-Dimethoxyphenyl)-3-(4-(4,4-dimethyl-2,6-dioxanyl) phenyl)cyclobutane (106)

To a 25 ml pear flask equipped with a magnetic stirrer was added 31.1 mg (0.082 mmol) of 3-(2,5-dimethoxyphenyl)-1-(4-(4,4-dimethyl-2,6-dioxanyl)phenyl)cyclobutene **100** and 10 mg (0.044 mmol) of platinum oxide. 5 ml of 10% ethyl acetate in ether was added. The flask was attached to a vacuum line, which was connected to a hydrogen cylinder. The reaction

flask was evacuated and flushed with hydrogen twice and then charged with a positive pressure of hydrogen. After 1 hour, the reaction mixture was removed from the hydrogen atmosphere, filtered, and evaporated to dryness on the rotary evaporator. Yield 30.8 mg (98.5%) of a colourless oil, which slowly crystallized. The product was recrystallized from ether/hexanes to give a white crystalline solid, mp = 98-100°C. ^{1}H NMR ($CDCl_3$): 0.78 (3H,s), 1.27 (3H,s), 2.16 (2H,dtt,J=11,10,3 Hz), 2.74 (2H,dtq,J=8,8,3 Hz), 3.47 (1H,ttd, J=9,7,3 Hz), 3.62 (2H,d,J=11 Hz), ca. 3.7 (1H,m), 3.75 (2H,d, J=11 Hz), 3.76 (3H,s), 3.76 (3H,s), 5.36 (1H,s), 6.67 (1H,dd, J=8,3 Hz), 6.75 (1H,d,J=8 Hz), 6.78 (1H,d,J=3 Hz), 7.23 (2H,d, J=8 Hz), 7.42 (2H,d,J=8 Hz); ^{13}C NMR ($CDCl_3$): 21.9 (CH_3), 23.1 (CH_3), 30.3 (C), 31.4 (CH), 36.3 (CH_2), 36.4 (CH), 55.7 (CH_3), 56.0 (CH_3), 77.7 (CH_2), 101.8 (CH), 110.5, 111.1, 113.9, 126.0, 126.5 (aromatic CH), 134.8, 136.1, 146.4, 151.8, 153.6 (aromatic C); observed m/e: 382 (14%), 164 (100%), 149 (14%); exact mass for $C_{24}H_{30}O_4$ calculated 382.21439, observed 382.21443

cis 5-(4-(3-(2,5-Dimethoxyphenyl)cyclobutyl)phenyl)-10,15, 20-tritolyl-porphyrin (108)

To a 250 ml round bottom flask equipped with a reflux condenser and a magnetic stirrer was added 23.1 mg (0.078 mmol) of cis 4-(3-(2,5-dimethoxyphenyl)cyclobutyl)benzaldehyde **64**, 1.0 ml (8.5 mmol) of p-tolualdehyde and 50 ml of propionic acid. This mixture was heated to reflux and 0.58 ml

(8.4 mmol) of freshly distilled pyrrole was added. The reaction mixture darkened upon the pyrrole addition. After 1 hour of reflux, the reaction mixture was cooled to room temperature and 30 ml of ethylene glycol was added. The reaction mixture was stored for 16 hours in a refrigerator. The crude product was collected by filtration and purified by chromatography on a 100 gm silica column, 1:1 methylene chloride:hexanes as eluent. The eluent was changed to pure chloroform once the majority of the tetratolylporphyrin (TTP) had been eluted from the column. TLC indicated the product band so isolated was approximately a 1:1 mixture of TTP and cis 5-(4-(3-(2,5-dimethoxyphenyl)cyclobutyl)phenyl)-10,15, 20-tritolyl-porphyrin (P4DMB) **108**.

The porphyrin material rich in P4DMB was combined with a similar fraction from the only other attempt of this reaction. The combined sample was purified by preparative thick layer chromatography on non-fluorescent silica, 1:1 methylene chloride:hexanes as eluent. Yield 14.2 mg (11.6% for both reaction attempts combined) of a purple solid. Due to the limited quantity of this material and the difficulty inherent in recrystallizing a highly coloured compound, this material was not further purified. ^{1}H NMR ($CDCl_3$): -2.75 (2H,s (broad)), 2.53 (2H,dtt,J=11,11,3 Hz), 2.70 (9H,s), 3.03 (2H,dtq,J=15,8,3 Hz), 3.83 (3H,s), 3.86 (3H,s), ca. 3.9 (1H,m), 4.22 (1H,m), 6.73 (1H,dd,J=8,3 Hz), 6.82 (1H,d,J=8 Hz), 6.99 (1H,d,J=3 Hz), 7.54 (6H,d,J=8 Hz), 7.62 (2H,d,J=8 Hz), 8.10 (6H,d,J=8 Hz), 8.14 (2H,d,J=8 Hz), 8.87 (8H,s);

^{13}C NMR ($CDCl_3$): 21.6 (CH_3), 31.6 (CH), 36.7 (CH_2), 36.7 (CH), 55.8 (CH_3), 56.1 (CH_3), 110.5, 111.2, 114.2, 124.9, 127.4, 134.6 (aromatic CH), 120.1, 120.2, ca. 130 (broad), 134.9, 137.3, 139.4, 139.8, 145.0, 151.9, 153.7 (aromatic C); observed m/e: 846 (100%), 682 (36%), 164 (2%); exact mass for $C_{59}H_{50}N_4O_2$ calculated 846.39335, observed 846.39193

m-Hydroxyacetophenone from m-methoxyacetophenone

To a 25 ml three necked pear flask equipped with a reflux condenser capped with a nitrogen inlet, a septum cap, and a magnetic stirrer was added 50 mg (0.33 mmol) of m-methoxy acetophenone and 10 ml of dry methylene chloride. The reaction mixture was cooled to -78°C and 1.0 ml (1.0 mmol) of a commercial 1.0 M solution of boron tribromide in methylene chloride was added. After 2 hours, the reaction mixture was warmed to room temperature. The reaction mixture was diluted with 25 ml of methylene chloride, washed with saturated sodium bicarbonate solution (25 ml), water (3 x 50 ml), and dried over anhydrous sodium carbonate. TLC analysis of the product revealed it to be mainly m-hydroxyacetophenone contaminated with residual starting material. The identity of the product was confirmed by comparison with an authentic sample.

cis 5-(4-(3-(2,5-Dihydroxyphenyl)cyclobutyl)phenyl)-10,15,20-tritolyl-porphyrin (109)

To a 25 ml three necked pear flask equipped with a reflux condenser capped with a nitrogen inlet, a septum cap, and a magnetic stirrer was added 6.9 mg (0.[illegible] mmol) of P4DMB **108** and 5 ml of dry methylene chloride. The reaction mixture was cooled to -78°C. 2.0 ml (2.0 mmol) of a commercial 1.0 M solution of boron tribromide in methylene chloride was added, in one portion. After 3 hours, the reaction mixture was warmed to room temperature, and diluted with 25 ml of methylene chloride. The reaction mixture was washed with saturated sodium bicarbonate (25 ml), water (3 x 50 ml), dried over anhydrous sodium carbonate, and evaporated to dryness on the rotary evaporator. The crude product was purified by preparative thick layer chromatography on silica, 5% methanol in benzene as eluent. Yield 3.6 mg (45%) of a purple solid. This material was not further purified. ^{1}H NMR ($CDCl_3$): -2.80 (2H,s (broad)), 2.54 (2H,dtt,J=8,8,3 Hz), 2.69 (9H,s), 3.04 (2H,dtq,J=11,11,3), 3.80 (2H,m), 4.44 (2H,s (broad)), 6.58 (1H,dd,J=8,3 Hz), 6.67 (1H,d,J=8 Hz), 6.83 (1H,d,J=3 Hz), 7.53 (6H,d,J=8 Hz), 7.59 (2H,d,J=8 Hz), 8.08 (6H,d,J=8 Hz), 8.12 (2H,d,J=8 Hz), 8.84 (8H,s); ^{13}C NMR ($CDCl_3$): 21.6 (CH_3), 31.2 (CH), 36.3 (CH_2), 36.6 (CH), 113.4, 114.4, 116.0, 124.9, 127.4, 134.6 (aromatic CH), 120.0, 120.1, ca. 131 (broad), 132.3, 134.6, 137.3, 139.3, 140.0, 144.5, 147.5, 149.6 (aromatic C); observed m/e: 818 (51%) 682 (100%); exact mass for $C_{57}H_{46}N_4O_2$ calculated 818.36205, observed 818.36080

Fluorescence Lifetime Measurements

Dilute solutions of TTP, P4DMB, $P4QH_2$ and P4Q were prepared in each of chloroform, methylene chloride, acetonitrile, benzene, n-butanol and benzonitrile. A flame sealed disposable pipette was used to scrape tiny quantities from the stock supply of P4DMB and $P4QH_2$ such that these solutions could be prepared. The P4Q solutions were prepared by oxidizing tiny quantities of $P4QH_2$ in methylene chloride with lead dioxide, filtering out the oxidant with a 1.2 μm millipore filter, evaporating the methylene chloride under a stream of nitrogen, and dissolving the residue in the appropriate solvent. The concentration of all solutions was adjusted such that the Soret absorbance was in the range 0.8 to 1.0 except TTP in acetonitrile and n-butanol. The poor solubility of TTP in these solvents limited the Soret absorbance to 0.1 in acetonitrile and 0.4 in n-butanol. All solutions were purged with nitrogen prior to analysis.

The fluorescence lifetimes of these solutions were measured using a PRA 3000 nanosecond spectrofluorimeter. A PRA model 510 hydrogen flash lamp, half height pulse width ca. 2 ns, operated at 30 KHz was used as the excitation source. The excitation monochromator was set to the maximum of the Soret. The emission monochromator was replaced by a Corning #2-58 cut off filter. The cut off for this filter is 640 nm. Typically 5×10^3 counts were collected in the peak channel. The results of these measurements are summarized in table 1-2.

Steady State Fluorescence Measurements

The solutions used for fluorescence lifetime determination were diluted with the appropriate solvents such that the Soret absorbance was ca. 0.05 These solutions were purged with nitrogen prior to analysis.

The steady state fluorescence spectra were recorded using a Perkin-Elmer 650-40 fluorescence spectrophotometer. The excitation monochromator was set to the maximum of the Soret. The emission monochromator scanned the 600 - 800 nm range. Integration of the total fluorescence intensity of these solutions allowed for determination of the fluorescence quantum yields. The results are summarized in table 1-4.

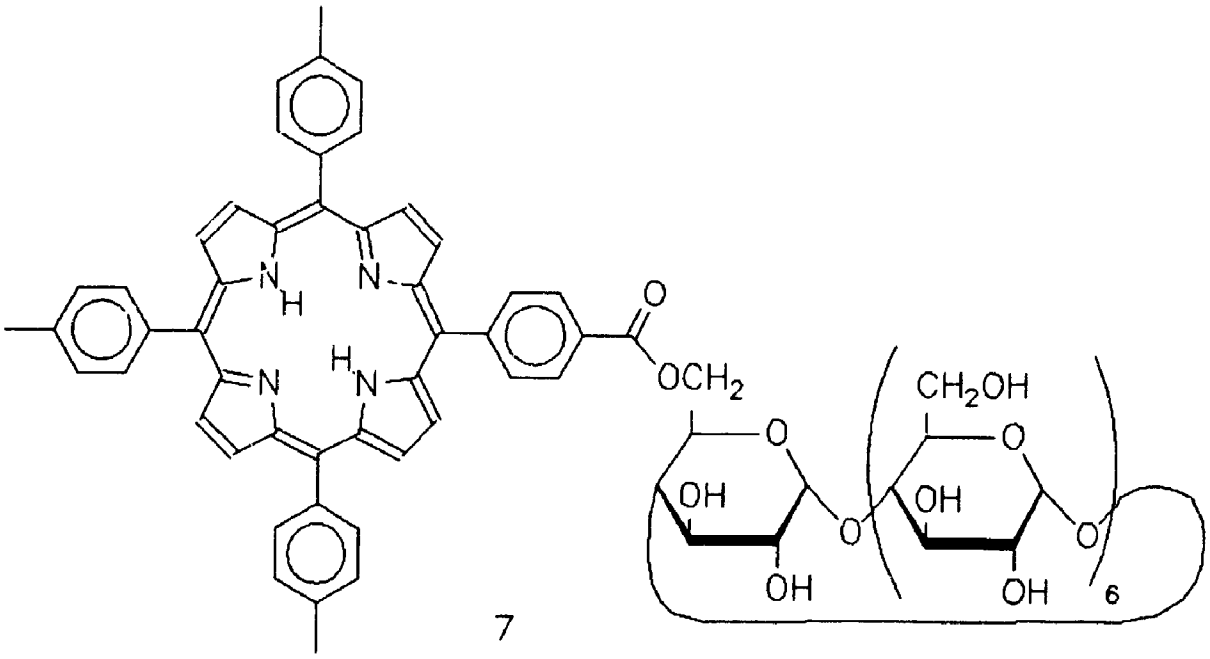
CHAPTER TWO: COMPLEXATION OF POTENTIAL ELECTRON ACCEPTORS WITHIN THE CAVITY OF A β-CYCLODEXTRIN LINKED TO A WATER SOLUBLE PORPHYRIN

(A) INTRODUCTION

As was seen in the previous chapter, the connecting linkage in species such as 62 plays a major role in photo-induced intramolecular electron transfer. In general, for the same donor and acceptor, shorter unsaturated linkages provide for more facile electron transfer than longer saturated linkages. A logical next question then becomes; what happens if the electron acceptor is changed?

To answer this question a series of compounds containing porphyrin donors covalently linked to different electron acceptors would be required. The task of synthesising such a series of compounds would not be trivial. One way to reduce the synthetic work required and yet obtain the maximum number of donor acceptor pairs was reported in 1984 by Gonzalez et al (6). This approach made use of the binding ability of β-cyclodextrin. The cyclodextrin which was covalently linked to the porphyrin donor (compound 7, Figure 2-1) acted to complex the electron acceptors. The cyclodextrin was thus acting as the connecting linkage, holding the electron acceptors close to the porphyrin and allowing for electron transfer. The advantages of using cyclodextrin as the connecting linkage were: the electron acceptors did not have to be formally bonded to the porphyrin thus reducing the synthetic workload, and, because cyclodextrins are capable of forming inclusion complexes with a wide variety of species, a large number of electron acceptors were able to be studied by the use of a single porphyrin-cyclodextrin species.

Figure 2-1: Compound 7



7

The ability of cyclodextrins to form inclusion complexes with a wide variety of species is a function of their macromolecular structure. Cyclodextrins are cyclic oligosaccharides of 6 or more D-glucopyranose units joined by alpha-(1,4) linkages to form a macrocyclic "doughnut shaped" structure, illustrated in Figure 2-2. Cyclodextrins are designated as α for the species with 6 D-glucopyranose units, β for 7 and γ for 3. The sides of this doughnut are not parallel but rather slope inwards toward the 6 position hydroxyl groups. The result is a conical shape with the 2 and 3 position hydroxyl groups at the wide end and the 6 position hydroxyl groups at the narrow end. The exterior of this doughnut is hydrophilic while the interior cavity, or hole, is relatively hydrophobic. The cavities of cyclodextrins are large enough to engulf small organic molecules, the dimensions of these cavities are listed in Table 2-1.

A cyclodextrin may form inclusion complexes with substrates which fit wholly or only partially within its cavity. That the substrate is not required to fully occupy the cavity is demonstrated by α-cyclodextrin. This has a cavity diameter of only 4.5 angstroms, and yet it forms a complex with adamantane, which is roughly spherical with a diameter of ca. 5.1 angstroms (66).

The stability of a cyclodextrin substrate complex is related to the fit of the substrate within the cavity; the more fully the substrate fits into the cavity the more stable the resulting complex. This is interpreted in terms of the

Figure 2-2: Structure and shape of cyclodextrins

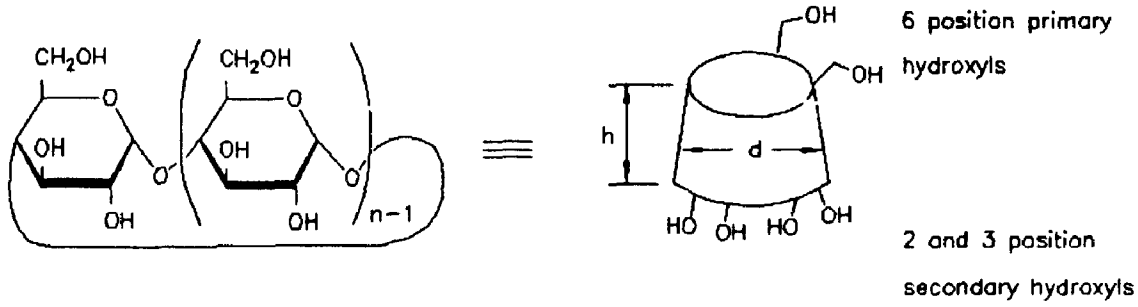


Table 2-1: Molecular dimensions of the cyclodextrins (65)

Cyclodextrin	Number of Glucose Residues n	Cavity dimensions (Å) Diameter d	Height h
Alpha	6	4.9	7.9
Beta	7	6.2	7.9
Gamma	8	7.9	7.9

substrate's ability to displace solvent molecules (in particular water) from the cavity (65,67,68). Substituting solvent in the cavity with a relatively hydrophobic substrate results in better solvation of both the substrate and the expelled solvent.

As stated above, the fit of the substrate within the cavity is the most important factor in determining a cyclodextrin's ability to form an inclusion complex with a given substrate; however, it is not the only factor. The ability of the substrate to hydrogen bond with the hydroxyl groups on the 2,3 and 6 positions of the cyclodextrin can also be important. This is illustrated by considering the binding of t-butanol and t-butyl hydroperoxide. The OH of the alcohol is relatively inefficient at hydrogen bonding with the cyclodextrin, due to steric hindrance, while the same is not true of the hydroperoxide OH. This explanation is used to rationalize the fact that the hydroperoxide forms a complex and that the alcohol does not (69). The hydrogen bonds formed between the substrate and the cyclodextrin can act to disrupt intramolecular hydrogen bonds within the cyclodextrin. This results in a release of strain energy in the macrocyclic ring (65,67,68), favouring the complex.

Cyclodextrin complexes have been detected by a number of techniques ranging from X-ray crystallographic studies to changes in the rate of reaction for included substrates. Some of the commonly applied methods of complex detection are UV-visible and fluorescence spectrophotometry and NMR

spectroscopy. The use of spectrophotometric techniques is based on the solvent dependent nature of the wavelengths and intensities of absorption and fluorescence (67,70,71). The relatively non-polar nature of the cavity provides significantly different "solvation" for the substrate than does the bulk solvent. The use of NMR spectroscopy to detect complex formation is similarly based on subtle changes associated with the change in "solvation". This change in "solvation" is reflected in small changes in chemical shift and/or changes in relaxation times (65,67,70).

Another method, of particular interest to this work, which has been used to detect complex formation is to monitor the quenching of the fluorescence of a fluorophore attached to the cyclodextrin (6). The observation of non Stern-Volmer kinetics indicates that as the quencher is added to the system it is bound in the cyclodextrin cavity, close to the fluorophore. This results in a high local concentration of quencher and the non-linear Stern-Volmer plot.

This is the approach that was used by Gonzalez et al (6) to study a number of potential electron acceptors. These workers were able to determine a threshold reduction potential for efficient electron transfer between the porphyrin and acceptors complexed with the cavity of cyclodextrin 7. Acceptors small enough to occupy the cyclodextrin cavity and with standard reduction potentials more positive than -0.3 V vs N.H.E. were found to be efficient. Electron acceptors with standard reduction potentials more negative than -0.5 V vs

N.H.E. and those too large to fit in the cyclodextrin cavity were found to be poor electron acceptors. This work was performed in DMSO and DMSO-glycerol solution.

We intended to extend this work to aqueous solution. There were two reasons for this: firstly the stability of a cyclodextrin complex is in part determined by the difference between the "solvation" of the substrate in bulk solvent and in the cavity, aqueous media will provide for a large difference and therefore more stable complexes; secondly water does not absorb in the visible and UV regions of the spectrum. This is desirable, since the cut off wavelength for water is < 200 nm it will not interfere in the spectroscopic methods used to measure the dissociation constants of the complexes.

Before beginning a discussion of the planned extension to the original report by Gonzalez et al. (6), a discussion of the methods by which the complex dissociation constant K_D can be determined is in order. K_D is defined by equation 2-1.

$$K_D = \frac{[\text{free cyclodextrin}]\ [\text{free substrate}]}{[\text{substrate-cyclodextrin complex}]} \qquad - (2\text{-}1)$$

The most common method of determining K_D is to use UV-visible spectrophotometry. The change in absorbance due to the substrate is monitored as the concentration of either cyclodextrin or substrate is varied. Benesi and Hildebrand (72) have described a treatment which allows the derivation

of a relationship between absorbance, concentration of substrate and complexing agent, and the dissociation constant K_D. This is expressed as equation 2-3, which is a simplification of equation 2-2.

$$\frac{d\ c_1\ c_2}{\Delta A} = \frac{K_D}{\Delta \epsilon} + \frac{c_1 + c_2 - c_3}{\Delta \epsilon} \qquad - (2\text{-}2)$$

where: c_1 and c_2 are the analytical concentrations of the substrate and cyclodextrin,
c_3 is the real concentration of the complex,
ΔA is the difference in absorbance between the substrate cyclodextrin solution and an equimolar solution of substrate free of cyclodextrin,
$\Delta \epsilon$ is the difference between the extinction coefficients for the free substrate and the complexed substrate,
d is the path length of the cell in which the absorbance measurements are made, and
K_D is the complex dissociation constant

if c_1 is set much larger than c_2, then c_2 and c_3 will be negligibly small and equation 2-2 will simplify to equation 2-3.

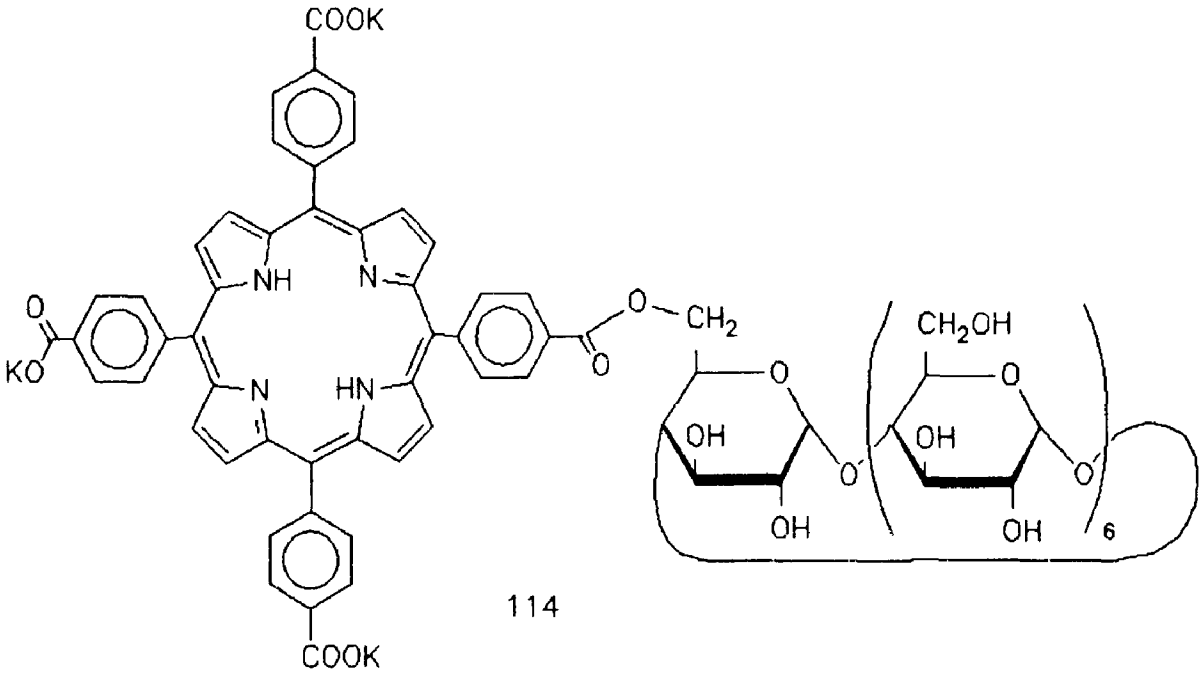
$$\frac{d\ c_1\ c_2}{\Delta A} = \frac{K_D}{\Delta \epsilon} + \frac{c_1}{\Delta \epsilon} \qquad - (2\text{-}3)$$

Using this relationship a linear plot of $(d\ c_1\ c_2)/\ A$ vs c_1 can be obtained and the constant K_D extracted.

Other procedures for the determination of K_D are based on essentially similar approaches in which either cyclodextrin or substrate concentration is varied and the change in a physical property monitored. The dissociation constant K_D is then extracted from a graphical representation of the data. Properties which can be monitored include: fluorescence emission from the substrate (71), optical rotation of the cyclodextrin (73), and nuclear magnetic resonances from either cyclodextrin or substrate (73).

The initially planned objective of the study described in this chapter was to synthesise compound **114**, a more water soluble analog of compound **7**, and to study electron transfer from the porphyrin to electron acceptors held within the cavity. This work, as stated previously, was intended to be performed in aqueous solvent in order to enhance the cyclodextrin-electron acceptor complex stability. The dissociation constants for these complexes were to be measured by independent means and the values used to quantify the electron transfer. However, it was anticipated that measurement of the dissociation constants for the cyclodextrin-substrate complexes, involving species **114** would be difficult due to the presence of the porphyrin chromophore. This chromophore blocks out all of the UV region and most of the visible region of the spectrum, effectively masking the absorption spectrum of the electron acceptors and making it impossible to determine K_D from substrate absorbance measurements. In addition it was anticipated that the

Figure 2-3: Compound **114**



114

porphyrin is too far removed from the cyclodextrin to be observably perturbed by complexation of substrates. For these reasons it was decided to measure dissociation constants for complexes in aqueous solution between potential electron acceptors and β-cyclodextrin. These dissociation constants would then be assumed to apply to **114** itself. This approach assumes that the presence of the porphyrin attached to the cyclodextrin will not affect the binding of a substrate within the cyclodextrin cavity.

It was hoped that the use of unsubstituted cyclodextrin as a model for **114** would allow for optical absorbance measurements to be used as the basis for determining the cyclodextrin-electron acceptor complex dissociation constants. It was anticipated that these values could be obtained by the method of Benesi and Hildebrand (72).

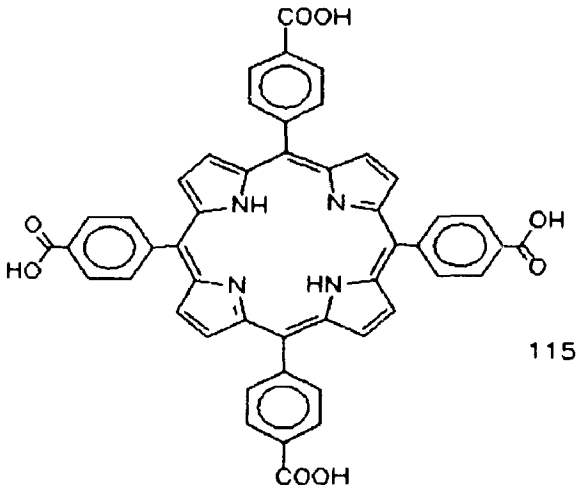
(B) RESULTS and DISCUSSION

i - Synthesis

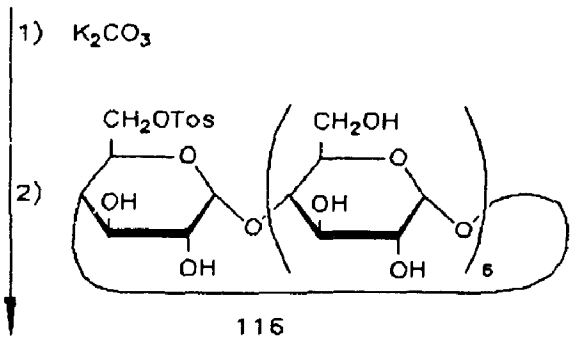
The synthetic approach to species **114**, outlined in Scheme 2-1, involves nucleophilic attack by one of the carboxylate groups of the potassium salt of 5,10,15,20-tetra-(p-carboxyphenyl) porphyrin **115** on mono-6-O-tosyl β-cyclodextrin **116**. This synthetic approach was chosen in order to ensure that only a single ester linkage was formed between the porphyrin and the cyclodextrin, and to avoid side reactions of the cyclodextrin ring. The more commonly used acid catalyzed methods of ester formation would not avoid these problems as they might result in more than one of the porphyrin carboxyl groups forming an ester linkage with the cyclodextrin. Alternatively, the porphyrin could become linked to more than one cyclodextrin, ultimately leading to the formation of a cross-linked polymer. Acid catalyzed conditions would also endanger the sensitive acetal functions of the cyclodextrin ring. The initial synthetic targets were therefore the porphyrin **115** and the substituted cyclodextrin **116**.

The porphyrin **115** (TCP) was readily prepared from pyrrole and p-carboxybenzaldehyde, which are both commercially available, following the procedure of Anton and Loach (33) as outlined in Scheme 2-2. The product was confirmed to be TCP by its ^1H NMR spectrum (CD_3OD) which showed only 5 signals: a 2 proton singlet at -3.02 ppm, upfield from TMS, assigned to the N-H protons in the center of the porphyrin ring. These protons normally appear at this high field due to the ring

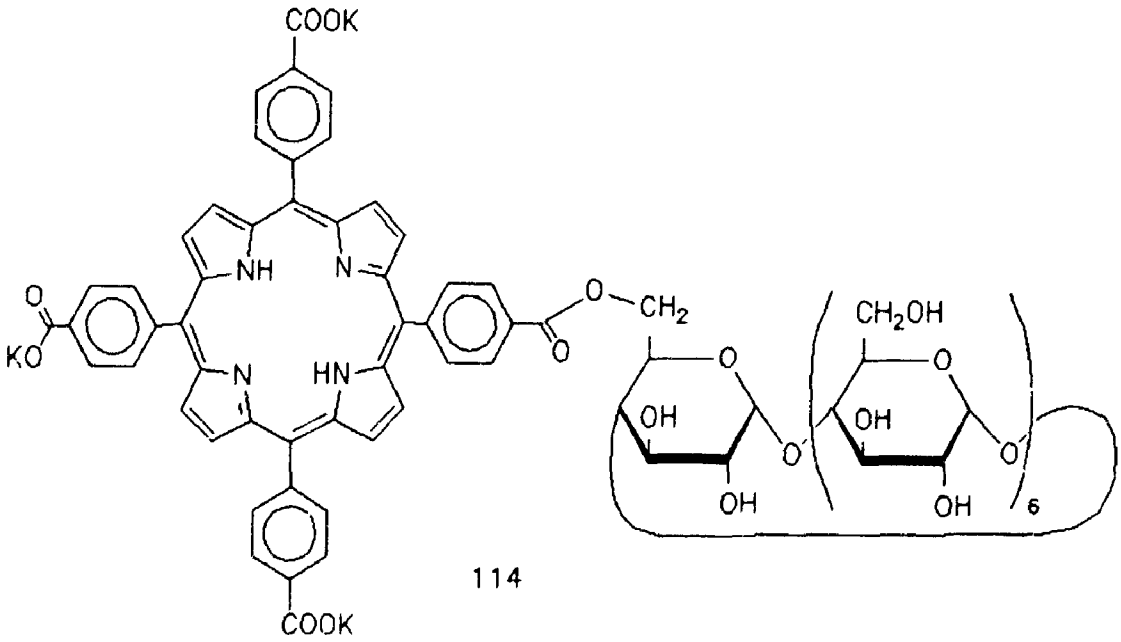
Scheme 2-1: Synthetic route to compound **114**


COOH
NH
N
N
HN
HO
O
OH
O
COOH

115

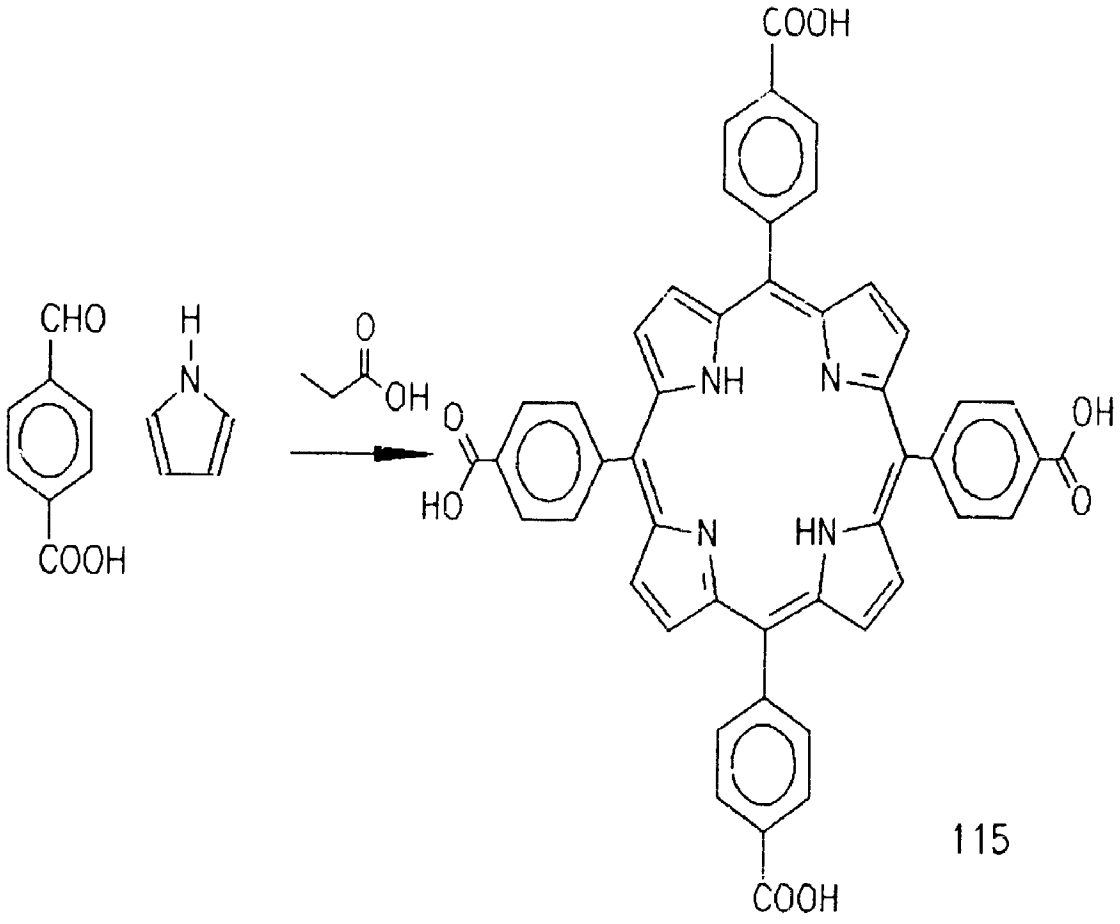

1) K_2CO_3
2)
CH_2OTos
CH_2OH
O
OH
OH
OH
OH
6

116


COOK
NH
N
N
HN
KO
O
O
CH_2
CH_2OH
O
OH
OH
OH
OH
6
COOK

114

Scheme 2-2: Synthetic route to compound 115

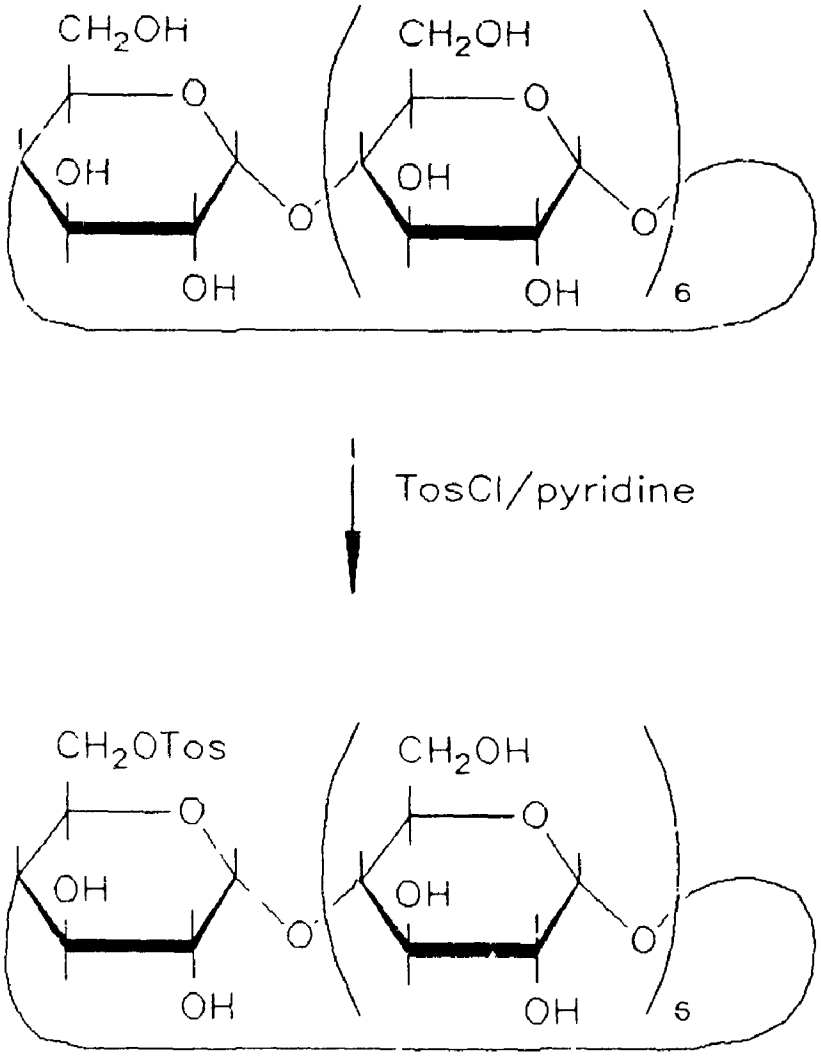


115

current associated with the porphyrin ring. A 4 proton singlet at 4.99 ppm assigned to CD_3OH arising from exchange with the carboxylic acid protons. Two 8 proton doublets, 8.47 ppm (J=8 Hz) and 8.65 ppm (J=8 Hz), assigned to the AB protons of the 4 phenyl rings, and a broad 8 proton singlet at 9.07 ppm assigned to the protons at positions 2,3,7,8,12,13,17 and 18 of the porphyrin ring. Infra-red analysis of the product revealed the aryl acid carbonyl stretch at 1680 cm^{-1}, consistent with compound **115**. The UV-visible spectrum of the product showed the Soret band at 414 nm and the presence of 4 Q-bands, indicative of a D_2h porphyrin. The potassium salt of **115** was easily prepared by treating TCP with an aqueous solution of potassium carbonate.

The mono-substituted cyclodextrin **116** was prepared by treating commercially available β-cyclodextrin with one equivalent of tosyl chloride in pyridine solution, as outlined in Scheme 2-3. This reaction is reported to yield the desired 6-O-tosyl compound and not the isomeric 2 or 3 position substituted products (74). That the desired 6-O-tosyl-β-cyclodextrin **116** was the isolated product was proven by NMR analysis. The proton NMR (DMSO solution) provided proof that only one tosyl group had been incorporated in the product. A 3 proton singlet at 2.43 ppm was assigned to the methyl group of the tosylate. A 14 proton multiplet at 3.31 ppm and a 26 proton multiplet at 3.58 ppm are assigned to the protons at positions 2,3,4,5 and 6 of the unsubstituted glucose rings and positions 2,3,4 and 5 of the glucose ring bearing the

Scheme 2-3: Synthetic route to compound **116**


CH2OH
CH2OH
O
O
OH
OH
O
O
OH
OH
6
TosCl/pyridine
CH2OTos
CH2OH
O
O
OH
OH
O
O
OH
OH
5

116

6-O-tosyl group. Two 1 proton multiplets at 4.24 and 4.37 ppm are assigned to the prochiral protons at position 6 of the glucose ring bearing the tosyl group. An exchangeable 6 proton multiplet at 4.52 ppm was assigned to the 6 position hydroxyl protons and an exchangeable 14 proton multiplet at 5.76 ppm was assigned to the 2 and 3 position hydroxyl protons. A 7 proton multiplet at 4.81 ppm was assigned to the protons at position 1 of the glucose rings. Two 2 proton doublets at 7.44 ppm (J=8 Hz) and 76 ppm (J=8 Hz) were assigned to the AB protons of the tosyl aromatic ring.

The C^{13} NMR spectrum of the product confirmed that the tosylation had occurred selectively at one of the 6 position hydroxyl groups. This spectrum was qualitatively similar to that reported by Gonzalez et al. (6) for compound 7. That is in addition to the CH_2 signal at 61.4 ppm and the CH signals at 73.7, 74.2, 74.5, 83.2 and 103.8 ppm which are associated with unsubstituted cyclodextrin several less intense signals were observed. Most notable among these being the CH_2 signal at 70.2 ppm and the CH signal at 70.5 ppm. These signals are respectively assigned to C-6 and C-5 of the glucose ring bearing the tosyl group, in agreement with the observations of Gonzalez et al. Other minor signals were observed at chemical shifts very similar to those of the larger signals, as anticipated. The signals due to the tosyl group were also present: 21.3 (CH_3), 128.2 (aromatic CH) and 130.0 (aromatic CH). The quaternary carbons of the tosyl group were not observed as the DEPT cross polarization technique was used to

obtain these spectra and this technique does not detect quaternary carbons.

The coupling of **116** and the salt of **115** to yield **114** was performed in refluxing dimethylformamide. The product isolated from this reaction was a shiny-black solid which was sparingly water soluble and showed the expected infrared and UV-visible absorptions. This product was homogeneous to chromatography on Sephadex G-25 and on silica gel, MeOH as eluent. However, this material could not be recrystallized and did not melt below 300°C. Further, attempts to measure the ^{1}H and ^{13}C NMR spectra of this material were unsuccessful due to its very limited solubility. Therefore, the structure of this material could not be confirmed. At this point, it had been determined that the dissociation constants for the complexes between β-cyclodextrin and the chosen electron acceptors could not be measured in water (see section ii). The study of the linked porphyrin cyclodextrin species **114** was, therefore, no longer of interest and consequently abandoned.

ii - Attempts to Measure Dissociation Constants

The electron acceptors chosen for this study were nitrobenzene, 2-nitrotoluene, 2-nitromesitylene, 1,2, 1,3 and 1,4 dinitrobenzene, anthraquinone and duroquinone. They have redox potentials ranging from -0.1 to -0.8V vs. NHE in aqueous systems (75,76). Comparison of these values with the previously established (6) range of quencher redox potentials

necessary for electron transfer from the singlet excited state of a tetra-aryl porphyrin suggested that it should be possible to detect electron transfer to at least some of these quenchers if they were complexed within the cavity of **114**.

As explained above, it was decided to attempt to measure the dissociation constants between these compounds and β-cyclodextrin in water and to use the latter as a model for **114**. The first attempts to measure the dissociation constants, K_D, of the β-cyclodextrin-quencher complexes in water were made by monitoring the change in UV absorbance of the quencher with a change in cyclodextrin concentration. The simplifying assumption of the Benesi-Hildebrand equation (72) requires that the concentration of one of the species involved in the complex be much less than that of the other. Accordingly, the cyclodextrin concentration was varied over the range 5×10^{-4} to 2×10^{-3} molar and the quencher concentration was set at 10^{-5} molar. When the resulting data were plotted according to equation 2-3 a very non-linear plot resulted. It was subsequently realized that the very small changes in absorbance which were detected were due to random errors and not due to complexation of the absorbing species.

Subsequent attempts to use UV-visible spectroscopy to measure K_D values utilized the quencher concentration as variable rather than the β-cyclodextrin concentration. Again, in order to satisfy the simplifying approximations of the Benesi-Hildebrand equation, the quencher concentration was set much higher than tnat of the cyclodextrin. However, as

was previously observed, changes in absorbance were very small and not systematic. Further trials in which both the quencher and cyclodextrin concentrations were large (in at least one trial both were close to the solubility limit) also resulted in very small non-systematic changes in absorbance. A major problem experienced in these experiments was the very poor solubility of the electron acceptors in water which served to reduce their ability to be complexed.

Due to the irreproducibility and random nature of the results of these experiments, it was decided to repeat an experiment already in the literature. Breslow (77) reports the dissociation constant for the complex between β-cyclodextrin and ferrocene in DMSO to be 20±4 mM. When this experiment was repeated a value of 20±8 mM was obtained. This suggested the possibility of making measurements in DMSO water mixtures and then extrapolating back to pure water. However, the large errors obtained from such an approach were found to severely limit the accuracy of K_D values so obtained.

The second approach to measuring the quencher-cyclodextrin K_D values was to monitor changes in the specific rotation of the plane of polarized light by cyclodextrin as the concentration of quencher was varied. However, the observed changes in specific rotation were found to be very small and, as with the previous approach, non-systematic. Again, the observed changes were due to random errors and not associated with complex formation.

The magnitude of the anticipated changes in optical density and in the specific rotation of the plane of polarized light associated with complexation can be calculated based on some reasonable assumptions. The maximum concentration of cyclodextrin substrate complex will be obtained when both cyclodextrin and substrate concentrations are maximized. The solubility limit of β-cyclodextrin in water is 0.016 M (65), to avoid possible problems associated with aggregation it was decided to limit the concentration of cyclodextrin in the solutions to 0.008 M. To satisfy the simplifying assumption of the Benesi-Hildebrand equation the concentration of the substrate was limited to 0.001 M. Assuming an extinction coefficient of 10^4 for the free substrate, this corresponds to an optical density of 1 using a 0.1 cm path length cell. If it is assumed that the dissociation constant for the cyclodextrin substrate complex is ca. 0.01 M in water (K_D for the β-cyclodextrin ferrocene complex in DMSO is 0.02 M (77)) then the maximum concentration of complex can be calculated to be ca. 4×10^{-4} M. If it is further assumed that the difference between the extinction coefficients for free and complexed substrate is ca. 5% (a 5% change in extinction coefficient was observed between free and complexed ferrocene in DMSO solution) then a calculation of the maximum change in absorbance upon complexation yields a value of 0.02 absorbance units. Although a change of this magnitude would be detectable if it were a change occurring in a single solution, these differences must be measured between independently

prepared solutions and this system is therefore prone to non-systematic errors. It should also be remembered that this change of 0.02 absorbance units represents an estimate of the largest possible change for this system. In practice the actual change associated with complexation may be much smaller. The failure of this approach to determine the dissociation constants can therefore be concluded to be due to random, non-systematic errors. Similarly, for the optical rotation measurements, it can be calculated that the maximum effect which could be expected is too small to measure accurately and reproducibly. Again, the failure of this approach is due to random, non-systematic errors.

The results of the optical absorbance and optical rotation measurements indicated that a more sensitive technique was required for determining K_D values. Fluorescence spectroscopy has been used to determine the dissociation constant for the N,N-dimethylaniline β-cyclodextrin complex in aqueous media (71). This work was repeated using cyclodextrin concentrations in the range $1 - 8 \times 10^{-3}$ M and N,N-dimethyl aniline concentration equal to 10^{-4} M. Large changes in the fluorescence intensity of N,N-dimethylaniline at 355 nm (excitation wavelength 263 nm) were observed. These changes were in agreement with those reported (71). It, therefore, appeared as if fluorescence measurements could be used to yield the desired K_D values. However, this method was found to be not applicable for use

with the substrates of interest as they were all found to be non-fluorescent.

The final technique used in an attempt to measure K_D values was NMR. A series of experiments were conducted in which the spectra of the substrate was monitored with increasing amounts of cyclodextrin. No changes in the substrate spectra were observed, even at high cyclodextrin:substrate ratios.

iii - Conclusions and Suggestions for Future Work

The poor solubility of β-cyclodextrin and of the potential electron acceptors resulted in very low concentrations of the complexes being formed in aqueous media. These low concentrations were not possible to measure accurately and therefore the K_D values for these complexes could not be determined. In addition the porphyrin-cyclodextrin **114** was very insoluble in water. It was therefore not possible to quantify the kinetics of porphyrin fluorescence quenching by electron acceptors held within the cyclodextrin cavity.

It may be possible to achieve the desired objectives of this project by one of two approaches: firstly, if a remote ionic substituent were added to the potential electron acceptors their solubility in water would be greatly increased. This would thereby allow for potentially much greater concentrations of complex and hence easier measurement of the K_D values. However, it is possible that the increased

solubility of these substrates in water would result in a significant increase in K_D with a corresponding decrease in the equilibrium concentration of complex resulting in no net increase in complex concentration. This potential problem and the fact that most of the substrates of interest are not commercially available with remote ionic substituents resulted in this approach not being tested.

The second possible solution to the problem of low complex concentration would be to replace β-cyclodextrin with the smaller alpha or the larger gamma cyclodextrins, both of which are much more soluble in water. This was not attempted for several reasons. Firstly the size of the cavity in alpha cyclodextrin may be too small to complex efficiently with some of the desired substrates. This would result in a variable distance from the porphyrin, bonded to the narrower 6-hydroxyl end of the cavity, to the substrate, partially inserted into the wider 2,3-hydroxyl end. This variable distance from donor to acceptor would affect the observed electron transfer rates, and thereby complicate the interpretation of the data. The larger cavity of gamma-cyclodextrin is sufficiently large to accommodate two acceptor molecules at the same time. Thus, the electron transfer to aggregates must be considered. This again serves to complicate the interpretation of the data. For these reasons, and the initial desire to compare the measured K_D values with the quenching studies previously reported by Gonzalez et al (6), the other cyclodextrins were not tested.

(C) EXPERIMENTAL

General

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-200 instrument. ^{13}C NMR spectra were recorded on a Varian XL-300 instrument. DEPT and APT spectra, also run on a Varian XL-300 instrument, were used to determine the multiplicities of the carbon signals. Infrared spectra were recorded on a Bruker IFS-32 instrument. Ultra-Violet and visible spectra were recorded on either a Cary 219 or a Hewlett-Packard 8450 instrument. Steady state fluorescence emission spectra were recorded on a Perkin-Elmer MPF4 instrument. Optical rotation measurements were made on a O. C. Rudolph & Sons model 80 polarimeter using the sodium D line at 589 nm.

Solvents were BDH or Fischer reagent grade, which were used as supplied, except tetrahydrofuran, which was dried over sodium/benzophenone. Water used for all dissociation constant measurements was double distilled.

Linked 5,10,15,20-tetra-(p-Carboxyphenyl)porphyrin β-Cyclodextrin (114)

To a 500 ml round bottom flask equipped with a reflux condenser and a magnetic stirrer was added 8.0 gm (10 mmol) of 5,10,15,20-tetra-(p-carboxyphenyl)porphyrin **115** and 240 ml of dimethylformamide. A solution of 2.4 gm (17 mmol, 0.85 eq)

of potassium carbonate in 160 ml of water was added. The reaction mixture was heated to reflux. After 3 hours reflux, the reaction mixture was evaporated to dryness on the rotary evaporator. The brown porphyrin salt residue was dried overnight under vacuum.

To a 25 ml pear flask equipped with a reflux condenser capped with a nitrogen inlet and a magnetic stirrer was added 0.35 gm (0.4 mmol) of the porphyrin salt and 2.0 ml of dry dimethylformamide. This solution was heated to 90C. A solution of 0.50 gm (0.4 mmol) of mono-6-O-tosyl-β-cyclodextrin **116** dissolved in 3.0 ml of dry dimethylformamide was added. The reaction mixture was stirred at 90C for 48 hrs. It was then evaporated to dryness on the rotary evaporator and dried overnight under vacuum. The crude product was purified by chromatography on 50 gm of Sephadex G-25 using water as eluent. Yield 0.26 gm (34%) of a black crystalline solid, mp > 300°C. All attempts to recrystallize this material or to recrystallize it as the free acid were unsuccessful. This material defied all attempts to measure its ^{1}H or ^{13}C NMR spectra. ir (KBr): 1711 cm^{-1}; UV (H_2O): 421(4.88), 519(3.99), 555(3.83), 592(3.69), 650(3.54)

5, 0,15,20-tetra-(p-Carboxyphenyl)porphyrin (115)

To a 1000 ml round bottom flask equipped with a reflux condenser and a magnetic stirrer was added 15.0 gm (0.1 mol) of p-carboxybenzaldehyde and 400 ml of propionic acid. This solution was heated to reflux. 7.2 ml (0.1 mol) of freshly

distilled pyrrole was added to the refluxing solution. The reaction mixture was refluxed 2 hours then cooled to room temperature and stored in the refrigerator overnight. The crude product was collected by filtration then washed with chloroform (2 x 100 ml). Yield 7.9 gm (40%) of a dark purple crystalline solid.

A small sample of the crude product was recrystallized from methanol/chloroform to yield a shiny purple crystalline solid, mp > 300°C. ^{1}H NMR (CD_3OD): -3.02 (2H,s), 4.99 (4H,s), 8.47 (8H,d,J=8 Hz), 8.65 (8H,d,J=8 Hz), 9.07 (8H,s(broad)); ir (KBr): 1680 cm^{-1}; UV (H_2O): 414(5.16), 520(3.81), 560(3.73), 596(3.56), 650(3.49)

mono-6-O-Tosyl-β-cyclodextrin (116)

To a 250 ml round bottom flask equipped with a nitrogen inlet and a magnetic stirrer was added 9.0 gm (7.9 mmol) of β-cyclodextrin, which had previously been dried in a vacuum oven for 24 hours, 1.5 gm (7.9 mmol) of p-toluenesulfonyl chloride (recrystallized from pet ether), and 135 ml of dry pyridine. The yellow coloured solution was stirred at room temperature for 2 hours. The reaction flask was then equipped for vacuum distillation. The apparatus was evacuated to 20 mm Hg and placed in an oil bath held at 40C. Once the pyridine had been removed, ca. 6 hrs, 200 ml of ether were added to the oily residue. This mixture was stirred at room temperature overnight. The crude product was then collected

by filtration. Yield 12.1 gm (118%) of a white crystalline solid which has a strong odour of pyridine.

A small sample of the crude product was twice recrystallized from water yielding a white crystalline solid, mp > 230°C (dec). ^{1}H NMR (DMSO d_6): 2.43 (3H,s), 3.31 (14H,m), 3.58 (26H,m), 4.24 (1H,m), 4.37 (1H,m), 4.52 (6H,m(exchangeable)), 4.81 (7H,m), 5.76 (14H,m(exchangeable)), 7.44 (2H,d,J=8 Hz), 7.76 (2H,d,J=8 Hz); ^{13}C NMR (pyridine d_5): 21.3 (CH_3), 61.2 (CH_2), 61.4 (CH_2), 70.2 (CH_2), 70.5 (CH), 73.7 (CH), 73.9 (CH), 74.2 (CH), 74.3 (CH), 74.5 (CH), 82.6 (CH), 83.2 (CH), 103.3 (CH), 103.8 (CH), 104.1 (CH), 128.2 (CH), 130.0 (CH)

Appendix 1: Basic Program for Mass Spectrum Analysis

```
100  PRINT "This program calculates the exact mass and the
     relative percentage of the m+1 and m+2 ions, and
     estimates the relative percentage of the m+3 and m+4
     ions."
110  PRINT " "
120  INPUT "Enter the  umber of carbon atoms";C
130  INPUT "Enter the number of hydrogen atoms";H
140  INPUT "Enter the number of nitrogen atoms";N
150  INPUT "Enter the number of oxygen atoms";O
160  INPUT "Enter the number of sulfur atoms";S
170  INPUT "Enter the number of chlorine atoms";CL
180  INPUT "Enter the number of bromine atoms";BR
190  EM=C*12+H*1.007825+N*14.00307+O*15.99491+S*31.97207+CL*
     34.96885+BR*78.9183
200  PRINT "The formula C";C;"H";H;"N";N;"O";O;"S";S;"Cl";CL;
     "Br";BR;"has an exact mass of";EM
210  MI=(.9889^C)*(.99985^H)*(.9963^N)*(.99759^O)*(.95^S)*
     (.7553^CL)*(.5054^BR)
220  M11=MI/.9889*C*.0111+MI/.99985*H*.00015+MI/.9963*N*.0037
     +MI/.99759*O*.00037+MI/.95*S*.0076
230  M21=MI/.99759*O*.00204+MI/.95*S*.0422+MI/.7553*CL*.2447
     +MI/.5054*BR*.4946
240  M2C=MI/.9889*C*.0111
250  M2CC=M2C*C/.9889*.0111*(((C^2)-C)/2)+M2C/.99985*H*.00015
     +M2C/.9963*N*.0037+M2C/.99759*O*.00037+M2C/.95*S*.0076
260  M2H=MI/.99985*H*.00015
270  M2HH=M2H*H/.99985*.00015*(((H^2)-H)/2)+M2H/.9963*N*.0037
     +M2H/.99759*O*.00037+M2H/.95*S*.0076
280  M2N=MI/.9963*N*.0037
290  M2NN=M2N*N/.9963*.0037*(((N^2)-N)/2)+M2N/.99759*O*.00037
     +M2N/.95*S*.0076
300  M2O=MI/.99759*O*.00037
310  M2OO=M2O*O/.99759*.00037*(((O^2)-O)/2)+M2O/.95*S*.0076
320  M2S=MI/.95*S*.0076
330  M2SS=M2S*S/.95*.0076*(((S^2)-S)/2)
340  M22=M21+M2CC+M2HH+M2NN+M2OO+M2SS
350  M3C=M2C/.99759*O*.00204+M2C/.95*S*.0422+M2C/.7553*CL*
     .2447+M2C/.5054*BR*.4946
360  M3H=M2H/.99759*O*.00204+M2H/.95*S*.0422+M2H/.7553*CL*
     .2447+M2H/.5054*BR*.4946
370  M3N=M2N/.99759*O*.00204+M2N/.95*S*.0422+M2N/.7553*CL*
     .2447+M2N/.5054*BR*.4946
380  M3O=M2O/.99759*O*.00204+M2O/.95*S*.0422+M2O/.7553*CL*
     .2447+M2O/.5054*BR*.4946
390  M3S=M2S/.99759*O*.00204+M2S/.95*S*.0422+M2S/.7553*CL*
     .2447+M2S/.5054*BR*.4946
400  M33=M2C+M3H+M3N+M3O+M3S
410  M4O=MI/.99759*O*.00204
420  M4OO=M4O*O/.99759*.00204*(((O^2)-O)/2)+M4O/.95*S*.0422
     +M4O/.7553*CL*.2447+M4O/.5054*BR*.4946
430  M4S=MI/.95*S*.0422
```

```
440  M4SS=M4S*S/.95*.0422*(((S^2)-S)/2)+M4S/.7553*CL*.2447
     +M4S/.5054*BR*.4946
450  M4CL=MI/.7553*CL*.2447
460  M4CLL=M4CL*CL/.7553*.2447*(((CL^2)-CL)/2)+M4CL/.5054*BR*
     .4946
470  M4BR=MI/.5054*BR*.4946
480  M4BRR=M4BR*BR/.5054*.4946*(((BR^2)-BR)/2)
490  M44=M4OO+M4SS+M4CLL+M4BRR
500  M1=M11/MI
510  M2=M22/MI
520  M3=M33/MI
530  M4=M44/MI
540  PRINT "The m+1/m ratio is";M1
550  PRINT "The m+2/m ratio is";M2
560  PRINT "The m+3/m ratio is";M3
570  PRINT "The m+4/m ratio is";M4
580  PRINT " "
590  INPUT "Do you wish to analyze another formula (y/n)";Q$
600  IF Q$="y" GOTO 110
610  END
```

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