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ISBN 0-315-46802-5

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

ABSTRACT

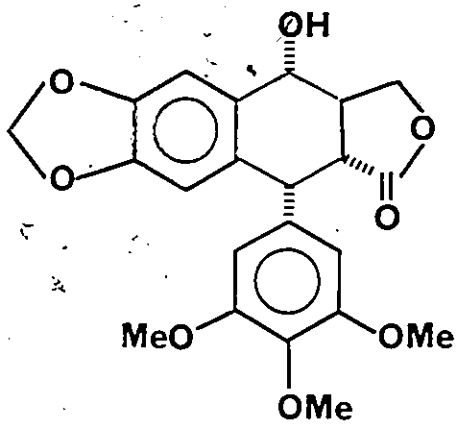
The first part of this thesis deals with an approach to the synthesis of podophyllotoxin analogues starting from ortho-benzyl benzaldehydes. An efficient method of synthesizing these types of aldehydes was developed. The proposed scheme is analogous to that utilized by D. Macdonald for the synthesis of podophyllotoxin. The scheme requires the aldehyde be converted to the hydroxy sulfone via irradiation in the presence of SO_2. Coupling with an appropriately substituted isocyanate would yield a urethane capable of undergoing an intramolecular Diels-Alder cyclization. The tricyclic compound thus formed could be converted via a sequence of steps to the desired analogue.

The second part deals with the attempts made in the synthesis of α- and β-peltatin. The methodology was based on the Glinski coupling reaction and modifications thereof involving a substituted benzaldehyde and a benzylic halide.

PART I

INTRODUCTION

The lignan lactone, podophyllotoxin 1, is the aglycone of the anticancer drugs Etoposide or VP-16 2 and Teniposide or VM-26 3. [1] Etoposide is currently in clinical use in North America, Europe, and Japan for treatment of a variety of human cancers such as leukemia, breast, and thyroid.



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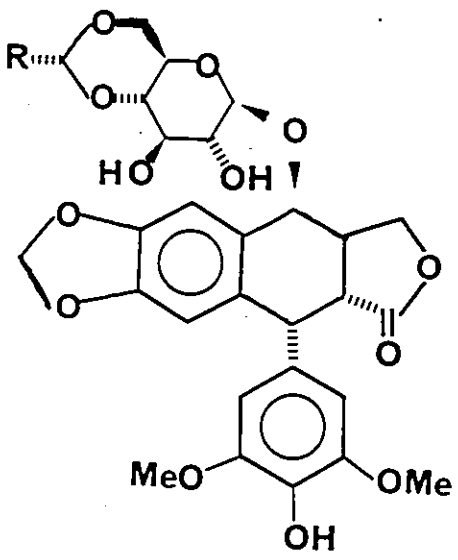

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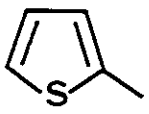
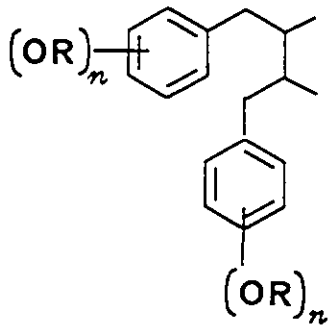
3, R = 

"Lignan" was a term first used by Haworth [2] to describe a class of optically active plant products which contain a 2,3-dibenzylbutane skeleton. They are assumed to be derived biogenetically by the dimerization of two aryl propane units at the β - carbon units of each of the two side chains. The skeletons of the resulting natural products can be represented by three structure types 4, 5, and 6.



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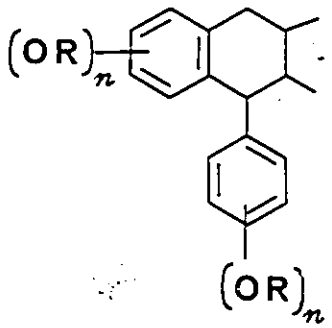

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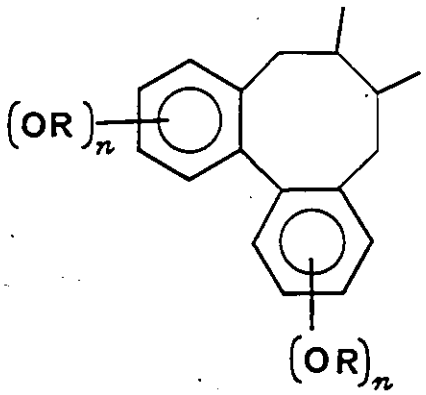


6

Lignans are abundant in the heartwood and resin of Coniferaceae. They have also been isolated in the wood, roots, seeds, and rhizomes of other plant families including Piperaceae, Oleaceae, and Berberidaceae.

Podophyllum is the dried roots and rhizomes of the podophyllum species (family Berberidaceae). Podophyllum peltatum Linnaeus, commonly known as the May Apple, American Mandrake, Indian Apple, Wild Lemon, or Duck's Foot, is found in North America.[3] Podophyllum emodi Wallich is the Indian counterpart and grows in the Himalayan Mountains. A third species growing in that region was discovered by Chatterjee and Mukerjee and is named Podophyllum sikkimensis R.Chatterjee and S.K. Mukerjee. These plants have been known for centuries for their medicinal and toxic properties.[3] When the podophyllum is extracted with alcohol the resin thus produced is called podophyllin or podophyllum resin. It was first prepared in 1835 by King.[4]

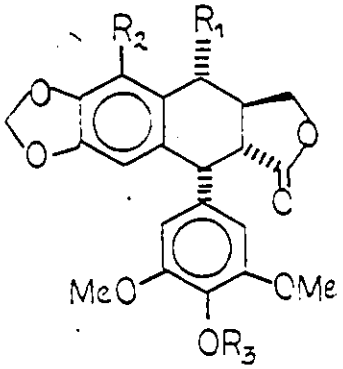
Podophyllum and podophyllin were used in the nineteenth century as cathartics and for various other medicinal purposes. Podophyllin was included in the United States Pharmacopeia from 1863 until it was removed in 1942.[5] In the latter year, Kaplan renewed interest in these compounds when he was able to cure the

venereal wart Condyloma Acuminatum.[6] Up-to 1960, podophyllin was studied as a possible agent for many clinical conditions.[7] However, the resin showed little, if any, therapeutic effect outside of Condyloma Acuminatum.

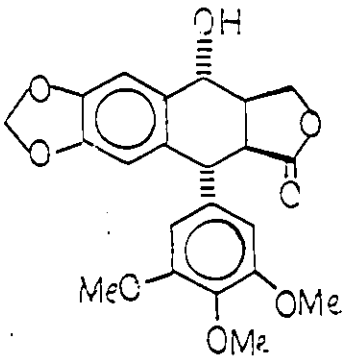
A number of researchers directed their efforts to the isolation and characterization of the constituents of podophyllin. Podophyllotoxin 1 , a white, crystalline substance, was first isolated by Podwyssotzki in 1880.[8] Between 1947 and 1950, Hartwell and workers isolated three new lignan lactones.[9,10,11] The peltatins (α - and β -) were isolated from Podophyllum Peltatum and 4'-demethylpodophyllotoxin was isolated from Podophyllum Emodi. By 1958, sixteen compounds (Table 1), ranging from flavonols to glycosylated lignans, had been isolated and identified.

In 1959, the structure and configuration of podophyllotoxin were established by Hartwell and Schrecker.[3] They postulated that the antimitotic and antitumor activities of the podophyllum lignans were closely related to their cis-(1:2)-trans-(2:3)-trans-(3:4) configuration, and also to its highly strained, trans-fused γ-lactone ring. Under mild base catalysis podophyllotoxin epimerizes to picropodophyllotoxin 15 which shows very little cytotoxic

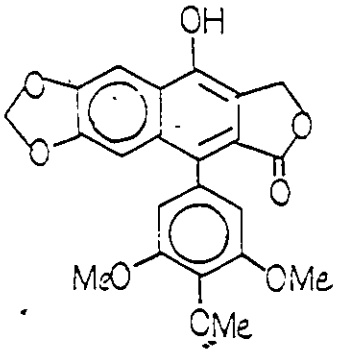
TABLE 1 : COMPOUNDS ISOLATED FROM PODOPHYLLIN



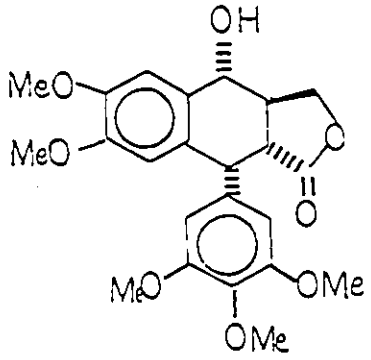
NAME	#	R_1	R_2	R_3
podophyllotoxin	1	OH	H	CH_3
α-peltatin	7	H	OH	H
β-peltatin	8	H	OH	CH_3
4'-demethylpodophyllotoxin	9	OH	H	H
deoxypodophyllotoxin	10	H	H	CH_3
podophyllotoxin glucoside	11	O-glucosyl	H	CH_3
α-peltatin glucoside	12	H	O-glucosyl	H
β-peltatin glucoside	13	H	O-glucosyl	CH_3
4'-demethylpodophyllotoxin glucoside	14	O-glucosyl	H	H



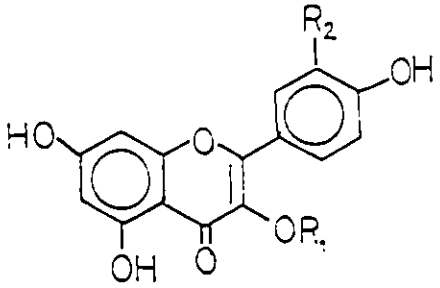
picropodophyllotoxin 15



tetradehydropodophyllotoxin 16



sikkimotoxin 17



NAME	#	R_1	R_2
quercetin	18	H	OH
isorhamnetin	19	H	OCH_3
quercetin 3-galactoside	20	galactosyl	OH
kaempferol	21	H	H

activity.[2a,34]

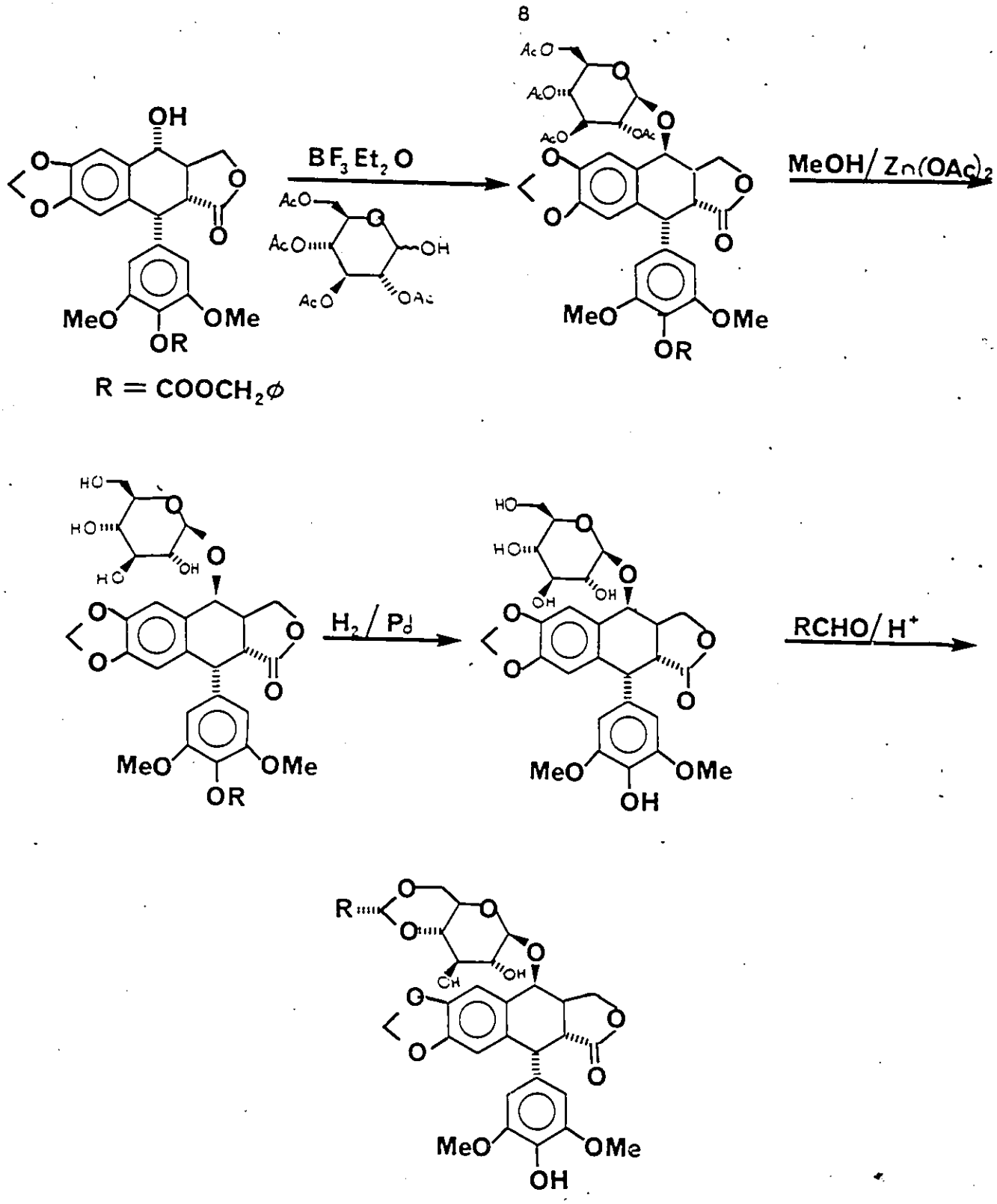
A scale Dreiding model of podophyllotoxin or the peltatins containing the trans-fused γ-lactone ring shows a strained inflexible molecule. A model of picropodophyllotoxin or of the peltatins containing the cis-fused lactone shows considerably less strain and rigidity and may exist in several fixed and interconvertible forms. In podophyllotoxin, the trimethoxyaryl ring is essentially perpendicular to the plane of the other rings whereas in the flexible picropodophyllotoxin this is so in only one of the conformations.

In 1950, Greenspan and coworkers investigated the effect of podophyllotoxin and the peltatins on transplanted tumors in mice.[12] The α-peltatin displayed the greatest activity. Encouraged by these results, α-peltatin was administered intravenously to patients with advanced neoplasms.[13] Some temporary response was observed but no long term activity was attained. The β-peltatin was also shown to be ineffective when oral doses were given to patients with leukemia and neuroblastoma.[14] Kuhn and von Wartburg of Sandoz Laboratories developed a method for synthesizing podophyllotoxin and epipodophyllotoxin glycosides (Scheme 1).[15,16] Clinical testing of both these structures gave

disappointing results. Further modification by converting the 4,6-diol of the glucoside into an acetal or ketal gave no dramatic increase in biological activity. However, removal of the 4'-methoxy group yielded a series of compounds which displayed a high in vitro activity against mouse lymphocytic leukemia L-1210.[17] Two of the derivatives were selected for clinical testing and were found to be very useful in treating a wide variety of cancers including bladder, brain, non-lymphatic leukemia, small-cell lung, breast, thyroid, and Hodgkin's disease. The compounds selected were 4'demethyl-1-O-(4,6-O-ethylidene- β -D glucopyranosyl) epipodophyllotoxin (VP-16 or "Etoposide") and 4'-demethyl-1-O-4,6-O-(2-thienylidene)- β -D-glucopyranosyl) epipodophyllotoxin (VM-26 or "Teniposide").[18]

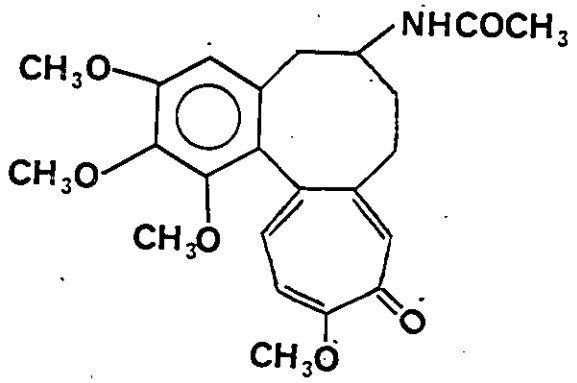
The activity of podophyllotoxin results from its interaction with microtubules [7,19] which are hollow, tubelike filaments essential for mitosis. Microtubules are formed by reversible polymerization of alternating α- and β - tubulin dimers into a helical array.

Since 1955, it has been known that colchicine 22 disrupted microtubule function and assembly, and as a result, the division of cells in metaphase is halted.[20] This results from the non-



SCHEME 1 PREPARATION OF EPIPODOPHYLLOTOXIN GLYCOSIDES

covalent binding of colchicine to a high-affinity binding site on tubulin which would prevent any tubulin polymerization. It was initially thought that this high-affinity site was also a binding site for podophyllotoxin as it too arrested metaphase and produced similar effects as the colchicine.[19] However, it was shown that the binding site for podophyllotoxin is not identical to that of colchicine but rather the two are overlapping. The overlapping site is thought to be where the trimethoxy aryl ring of both compounds binds.[21]



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Flow cytometry studies indicate that Etoposide and Teniposide delay the transit of cells through the late S or early G_2 phase of the cell cycle.[22,23] Thus, they possess a mechanism of action different from podophyllotoxin.

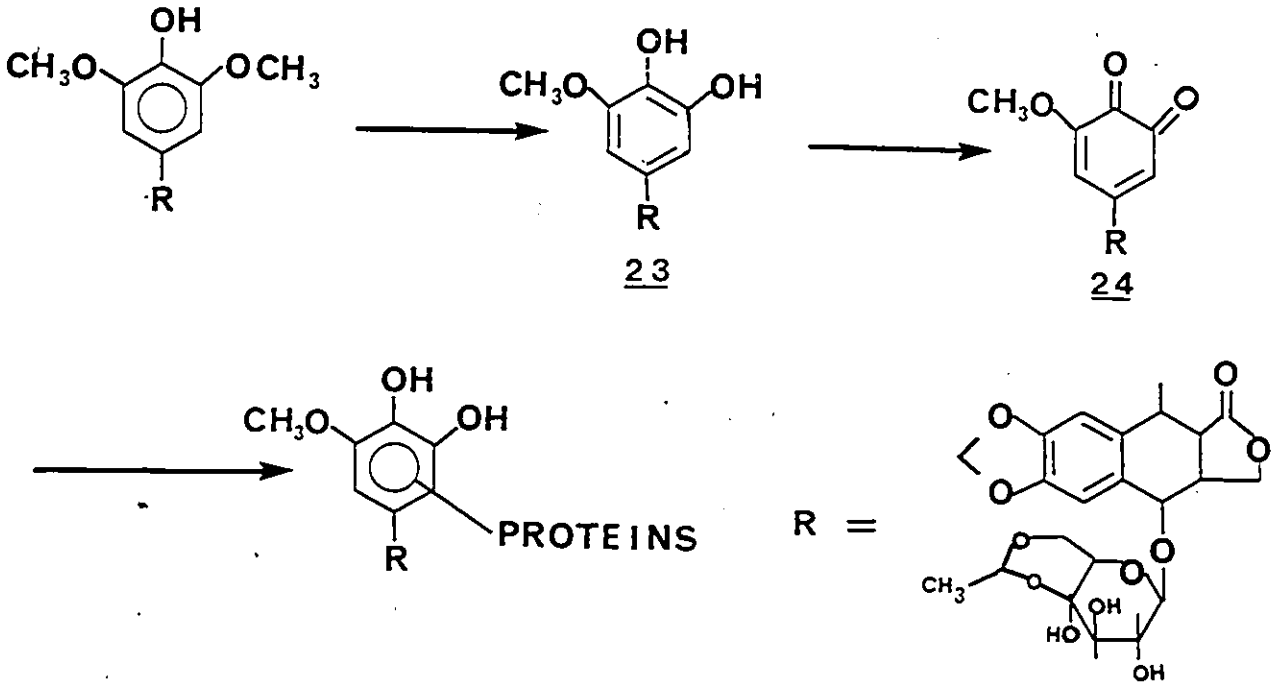
It has been proposed that the antitumor effects of VM-26 and VP-

16 result from their ability to induce DNA breakage. Several groups have shown that Etoposide does induce damage in mouse L-1210 and human lung adenocarcinoma cells.[24,25,26]

Evidence suggests that DNA topoisomerase II, an enzyme that breaks and rejoins DNA strands, mediates this DNA cleavage.[27] It is believed in the presence of the epipodophyllotoxins a complex is formed between the enzyme and DNA by intercalation which, when exposed to a denaturing agent, results in cleavage of the DNA strands.[28] This hypothesis is supported by the work of Rowe and coworkers.[29]

Sinha and workers [31] studied the activity of Etoposide by incubating VP-16 with mouse liver microsomes in the presence of NADPH. This incubation resulted in O-demethylation of the 3'-methoxy group. This O-demethylation would result in the o-hydroxy derivative 23 which could be oxidized to the o-quinone 24 (Scheme 2). Such an o-quinone could bind to cellular macromolecules and result in cytotoxicity. In this study, VP-16 was also found to be an inhibitor of microsomal lipid peroxidation while the parent podophyllotoxin had little effect on this peroxidation. From their data the authors suggested that both a 4'-hydroxyl group and an adjacent oxygen substituent was essential for cytotoxicity. In

another study [30] it was shown that VP-16 forms an oxygen-centered free radical of unknown structure when activated by horseradish peroxidase in the presence of hydrogen peroxide. This species too could bind to cellular components and result in cell destruction. Their most recent study [32] demonstrates that an active intermediate of VP-16 does bind irreversibly to both DNA and microsomal proteins. Whether it is the free radical species (or a derivative) or the o-quinone structure which binds to cell macromolecules is not known. These studies, however, lead one to believe that these types of binding may play a major role in the activity of the epipodophyllotoxins.



SCHEME 2 PROPOSED METHOD OF ETOPOSIDE ACTIVITY

In order to examine the validity of these suggestions and possibly gain some insight into the mode of action of these compounds it was decided to synthesize analogues with different oxygen substitution patterns in rings B and E. Ideally, the synthetic sequence would be versatile and efficient to enable one to prepare sufficient quantities of several analogues for biological investigation.

At the time this work was begun only three syntheses of podophyllotoxin had been reported. The first two by Gensler [33,34] and by Kende [35] were considered unsuitable since they produced the epimeric picropodophyllotoxin. This required an inefficient epimerization to produce the trans-fused- γ -lactone of podophyllotoxin. Their syntheses are shown in Scheme 3 and Scheme 4. Furthermore, separation of the podophyllotoxin from the picropodophyllotoxin thus produced requires careful column chromatography and there was no guarantee that analogues of the two compounds would be separable.

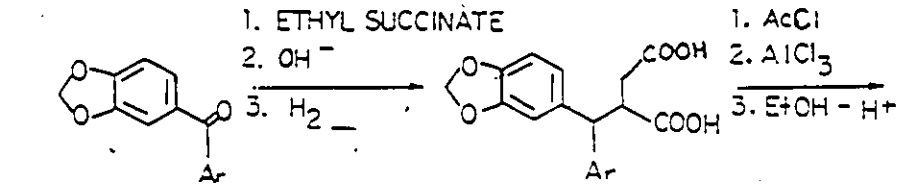
The Rodrigo synthesis [36] published in 1980 avoided the above contra-thermodynamic epimerization and is in principle suitable for the preparation of podophyllotoxin analogues. The synthesis is shown in Scheme 5. Lithiation of 6-bromopiperonal dimethyl acetal

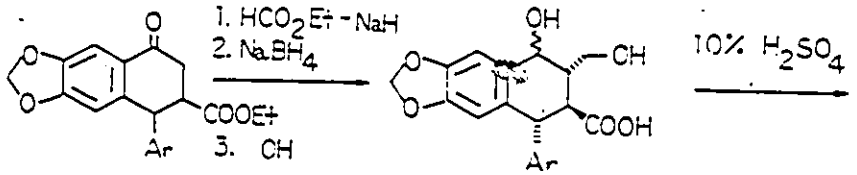
followed by reaction with 3,4,5-trimethoxybenzaldehyde afforded the hydroxy acetal 25.[37] The isobenzofuran derivative 26 was formed from 25 by treatment with acetic acid in situ. Subsequent trapping by dimethyl acetylenedicarboxylate yielded 27. Catalytic hydrogenation, epimerization, and ester reduction resulted in the formation of the bicyclic hydroxy ester 28. Upon hydrogenation, the tetralin 29 was produced and converted to an acetonide. Subsequent saponification to give the acid 30 followed by acid treatment gave (±)-neopodophyllotoxin 31.[38] This was converted to podophyllotoxin 1 by opening the lactone ring to give the acid and relactonization with DCC.[39] The overall yield of podophyllotoxin after twelve steps was 11%.

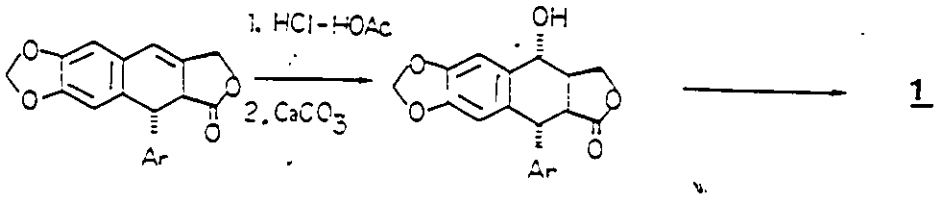
In the Rodrigo synthesis replacement of either 6-bromopiperonal dimethyl acetal or the trimethoxy benzaldehyde by analogues in the first step would lead to podophyllotoxin analogues. This synthesis apparently satisfies both criteria of versatility and efficiency.

A project directed toward a new synthesis of podophyllotoxin was nearing completion and has since been completed by Dwight Macdonald in our laboratories (Scheme 6).[40] Data available suggested that it would have a versatility similar to that of the Rodrigo

synthesis and would require a similar number of steps. It was decided to attempt the preparation of analogues following the Macdonald route or a variation thereof.







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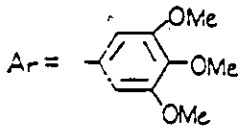
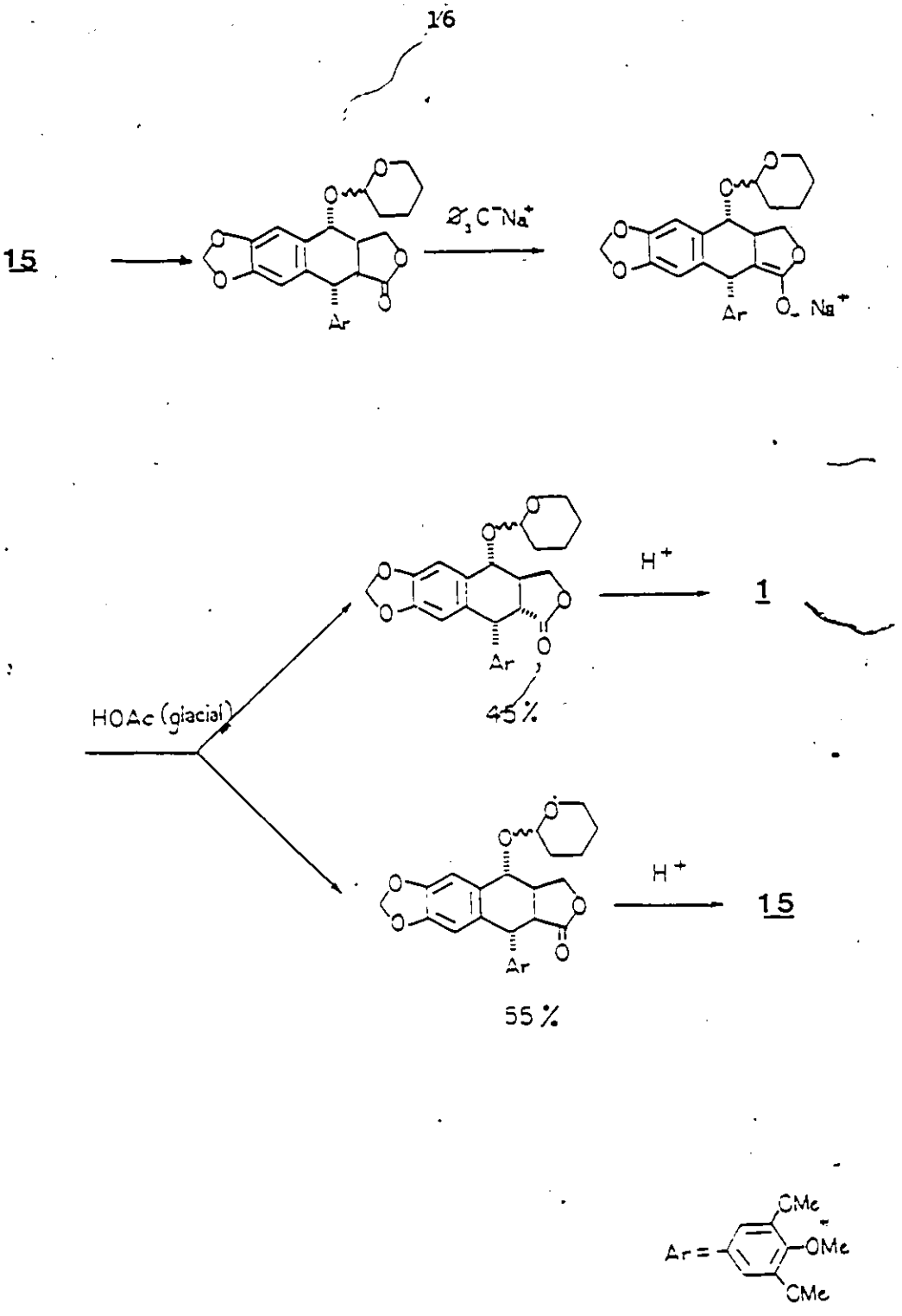
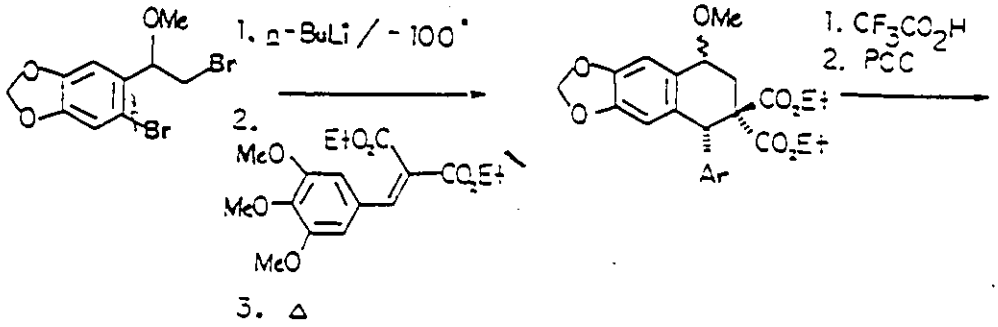
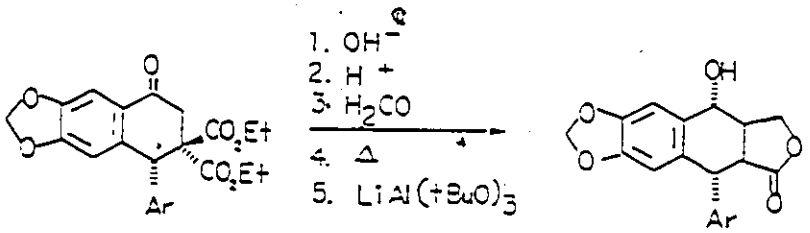


SCHEME 3 GENSLER'S SYNTHESIS OF PODOPHYLLOTOXIN



SCHEME 3 GENSLER'S SYNTHESIS OF PODOPHYLLOTOXIN (cont.)





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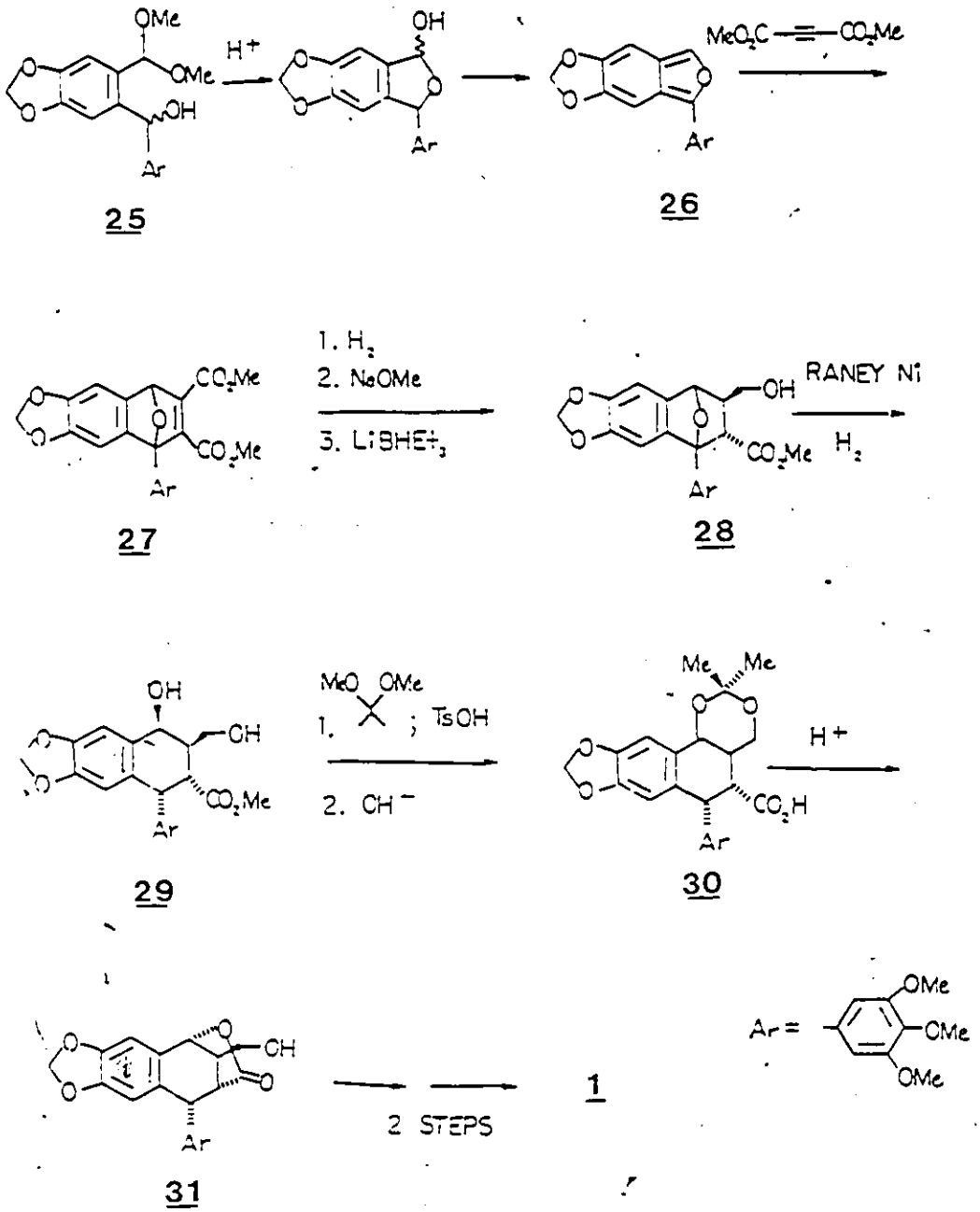
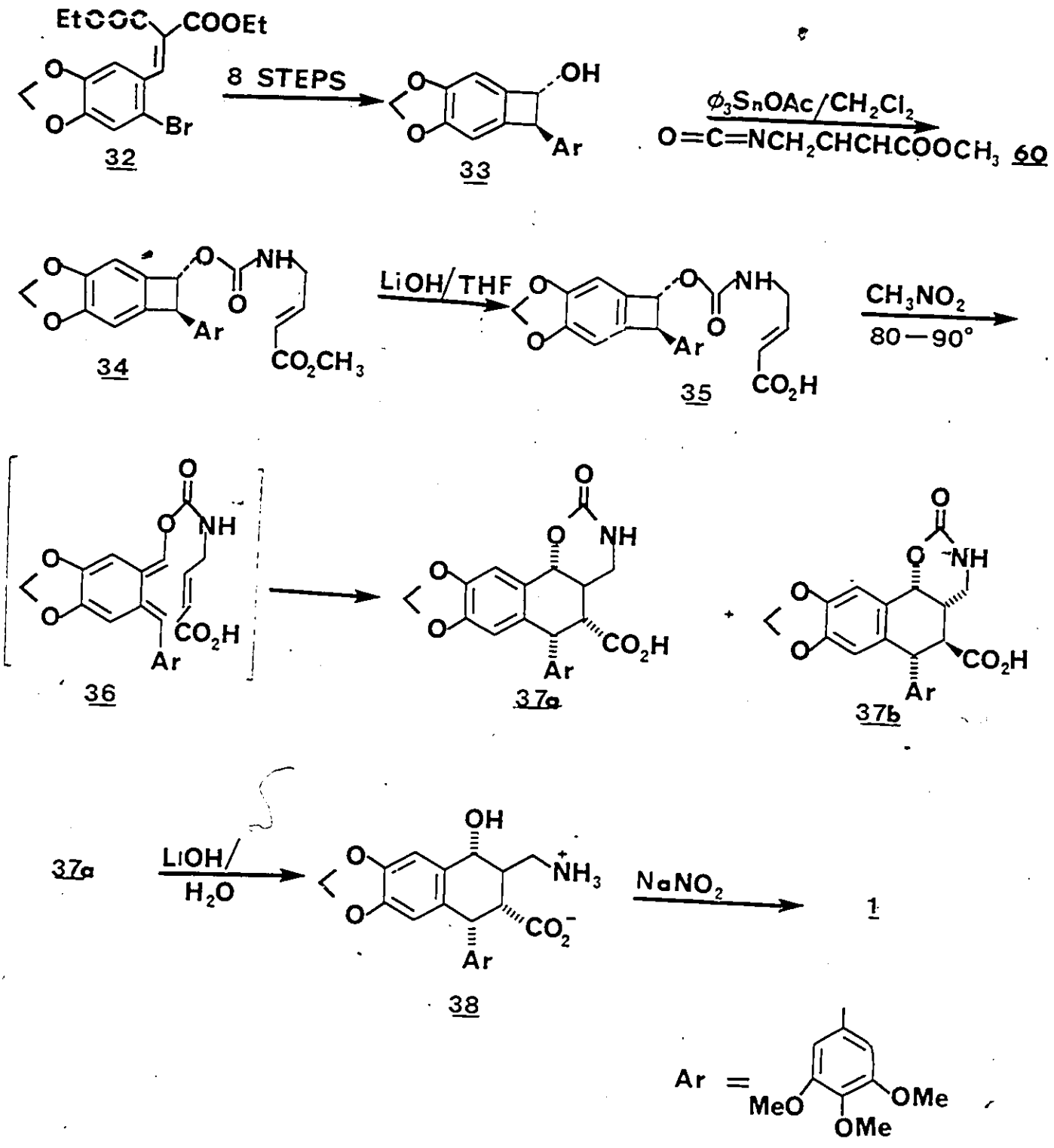
1. t-BuMe$_2$SiCl / IMIDAZOLE
2. LDA
3. PY·HCl
4. NEt$_3$·HF

→ 1 + 15 1 : 1

SCHEME 4 KENDE'S SYNTHESIS OF PODOPHYLLOTOXIN



SCHEME 5 RODRIGO'S SYNTHESIS OF PODOPHYLLOTOXIN



SCHEME 6 MACDONALD'S SYNTHESIS OF PODOPHYLLOTOXIN

RESULTS AND DISCUSSION

The Macdonald and Durst synthesis (Scheme 6) of (±)-podophyllotoxin required the initial preparation of a trans-2-arylbenzocyclobuten-1-ol 33 which was prepared via an eight step sequence from the diester 32.[41]

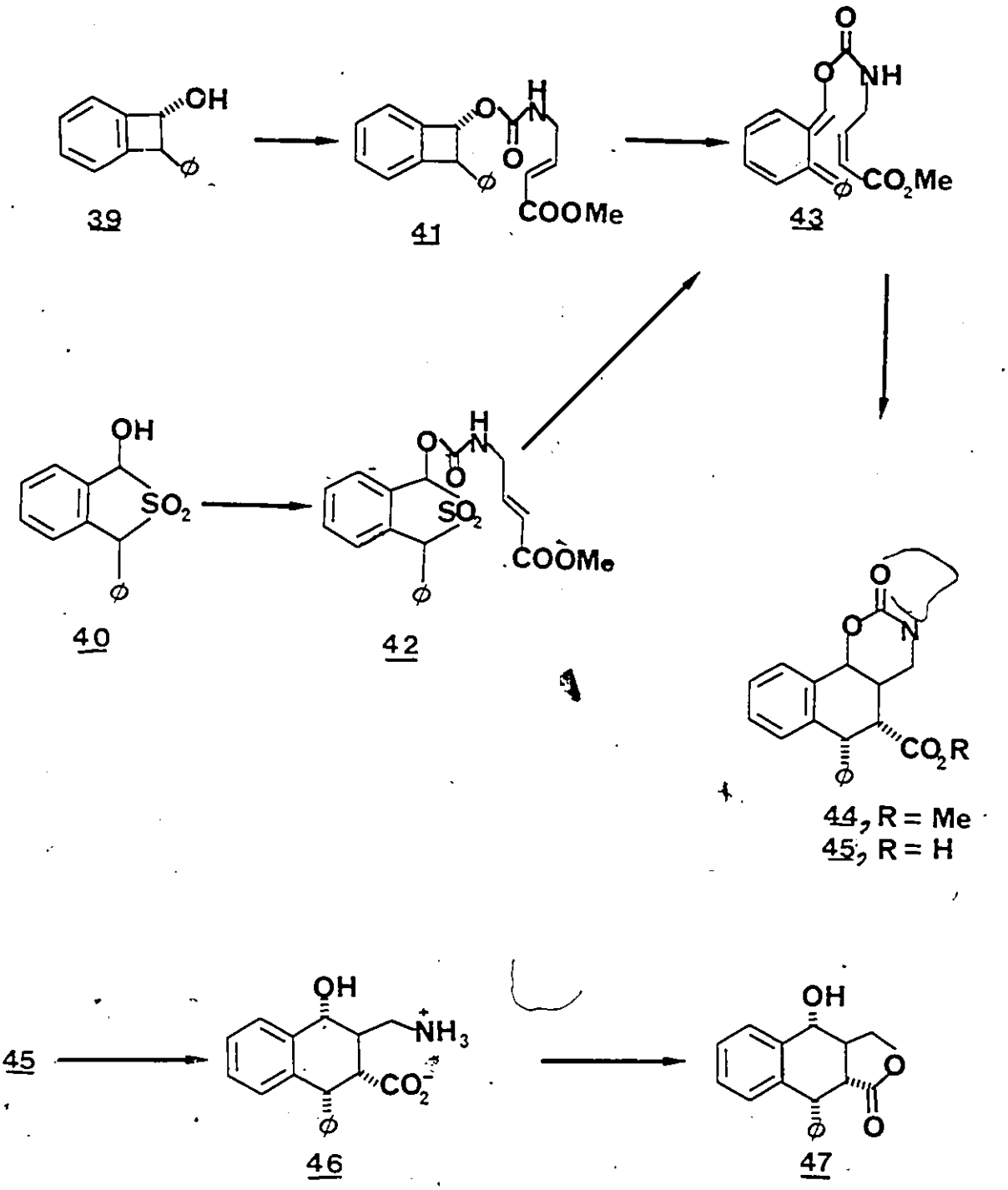
The appropriate cyclobutenol (trans-2-(3',4',5'-trimethoxyphenyl)-4,5-methylenedioxybenzocyclobutyl alcohol) was converted to a urethane 34 by reaction with the isocyanate of methyl-4-aminocrotonate [42] in methylene chloride using triphenyltin acetate, a mild Lewis acid, as the catalyst.[43] The connection between the benzocyclobutenol and the crotonate ester would ensure the desired regiochemistry in the Diels-Alder reaction and should generate all four chiral centres in podophyllotoxin in a single step. The nitrogen function of the urethane could also prove useful in the final γ-lactone construction. This connection could have been made via a variety of functional groups such as a mixed carbonate or mixed acetal. However, the preparation of these latter compounds usually requires basic reaction conditions which are not tolerated by the trans-2-arylbenzocyclobutenol.

Hydrolysis of the methyl ester 34 was performed using an

aqueous solution of lithium hydroxide in tetrahydrofuran to yield the acid 35. Hydrolysis was necesssary prior to the thermolysis since hydrolysis of the tricyclic methyl ester caused considerable epimerization at C-2 and thus eventually yielded a mixture of podophyllotoxin and picropodophyllotoxin.

Heating the acid 35 in nitromethane at 80-90° afforded the intermediate o-quinodimethane 36 via a conrotatory opening of the cyclobutene ring. A subsequent intramolecular Diels-Alder reaction gave a 5:1 mixture of the tricyclic acids 37a and 37b. Hydrolysis of the urethane was carried out with lithium hydroxide in aqueous THF and gave the amino acid 38 without epimerization at C-2. Thus the epimerization observed above occurred prior to the conversion of the methyl ester into its carboxylate salt. The amino acid was diazotized with sodium nitrite at pH=4 to give directly (±)-podophyllotoxin with an overall yield of 11% from trans-2-(3',4',5'-trimethoxyphenyl)-4,5-methylenedioxybenzocyclobutyl acetate.

It was also demonstrated by Macdonald that the tricyclic urethane 37 suitable for the synthesis of a podophyllotoxin analogue devoid of aromatic substituents could be prepared from either trans-2-phenylbenzocyclobutenol 39 or cis-1-hydroxy-3-phenyl-

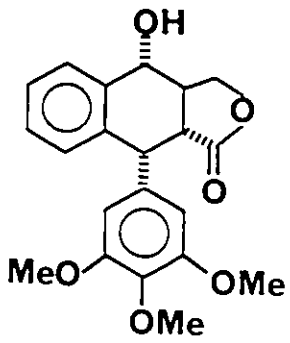


SCHEME 7 MACDONALD'S SYNTHESIS OF PODOPHYLLOTOXIN ANALOGUES

1,3-dihydro-benzo[c]thiophene-2,2-dioxide 40 (Scheme 7). The cis sulfone 40 is available in one step via the photolysis of 2-benzylbenzaldehyde in the presence of sulfur dioxide. The urethanes 41 and 42 were derived from 39 and 40 via the isocyanate coupling reaction described above. Thermolysis of the cis-urethane sulfone 42 resulted in a suprafacial cheletropic loss of sulfur dioxide to yield the o-quinodimethane derivative 43; this intermediate was also formed upon heating 41 to 100°. A subsequent Diels-Alder reaction resulted in the formation of the tricyclic ester 44, which upon demethylation with lithium iodide in DMF gave the acid 45. The urethane ring was then hydrolyzed with lithium hydroxide in aqueous THF to afford the amino acid 46 which was diazotized to give the podophyllotoxin analogue 47.

For this thesis, we chose to prepare the podophyllotoxin analogues 48 and 49 utilizing the hydroxy sulfone route. This sequence would require the fewest steps from the appropriately o-substituted benzaldehyde to a podophyllotoxin analogue.

The podophyllotoxin analogues we had hoped to prepare were chosen on the basis of the data available on the mechanism of action of Etoposide presented earlier. Since the methylenedioxy functionality on the B ring does not appear to have any direct



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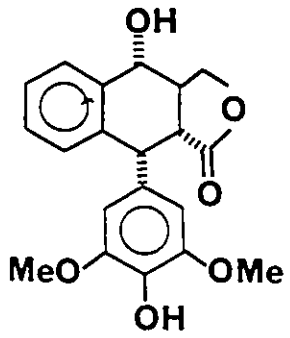


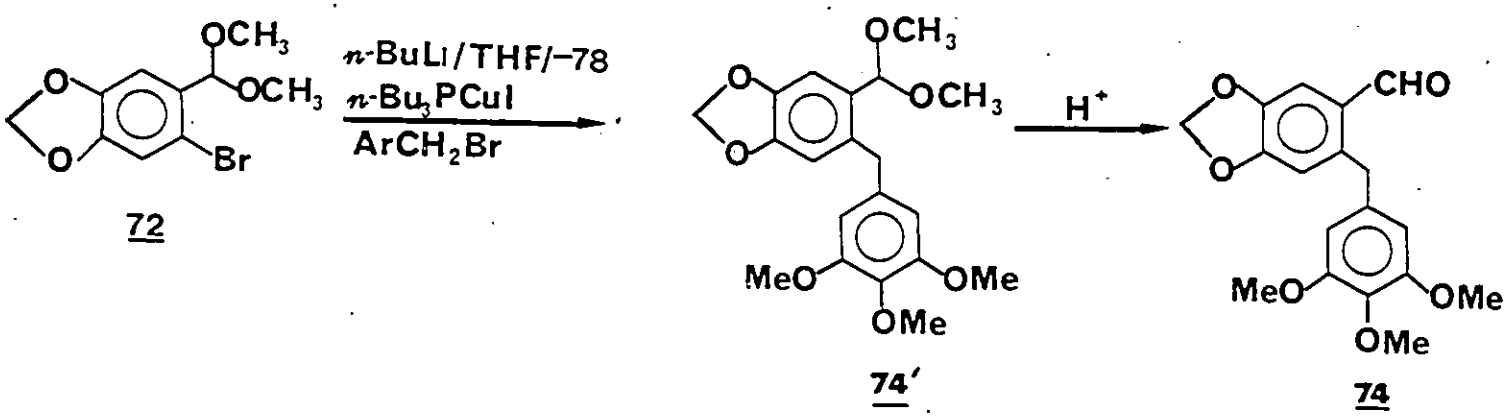
49

correlation to the activity of Etoposide, it was not included in the B ring of our proposed analogues. In 49, the 4'-methoxy group was replaced by a hydroxyl group since biochemical studies indicate that a 4'-hydroxy group on the E ring is essential for cytotoxicity.

The starting materials for our proposed synthesis of certain podophyllotoxin analogues are specifically substituted ortho-benzyl benzaldehydes. A search of the literature showed that a reliable multigram preparation of these compounds needed to be developed.

Glinski developed a cuprate route (Scheme 8) to these types of ortho substituted benzaldehydes and claimed an overall yield of 84% of 74 based on, and starting from 6-bromopiperonal dimethyl acetal.[44] Attempts to repeat this reaction gave variable results, in particular, when performed on gram-scale quantities.

Very recently, Charlton and Alauddin [45] published a synthesis of 6-(3,4-dimethoxybenzyl)-veratraldehyde using a modification of the Glinski coupling. These authors also report problems with reproduciblity and could carry out the reaction on no more than a one gram scale.

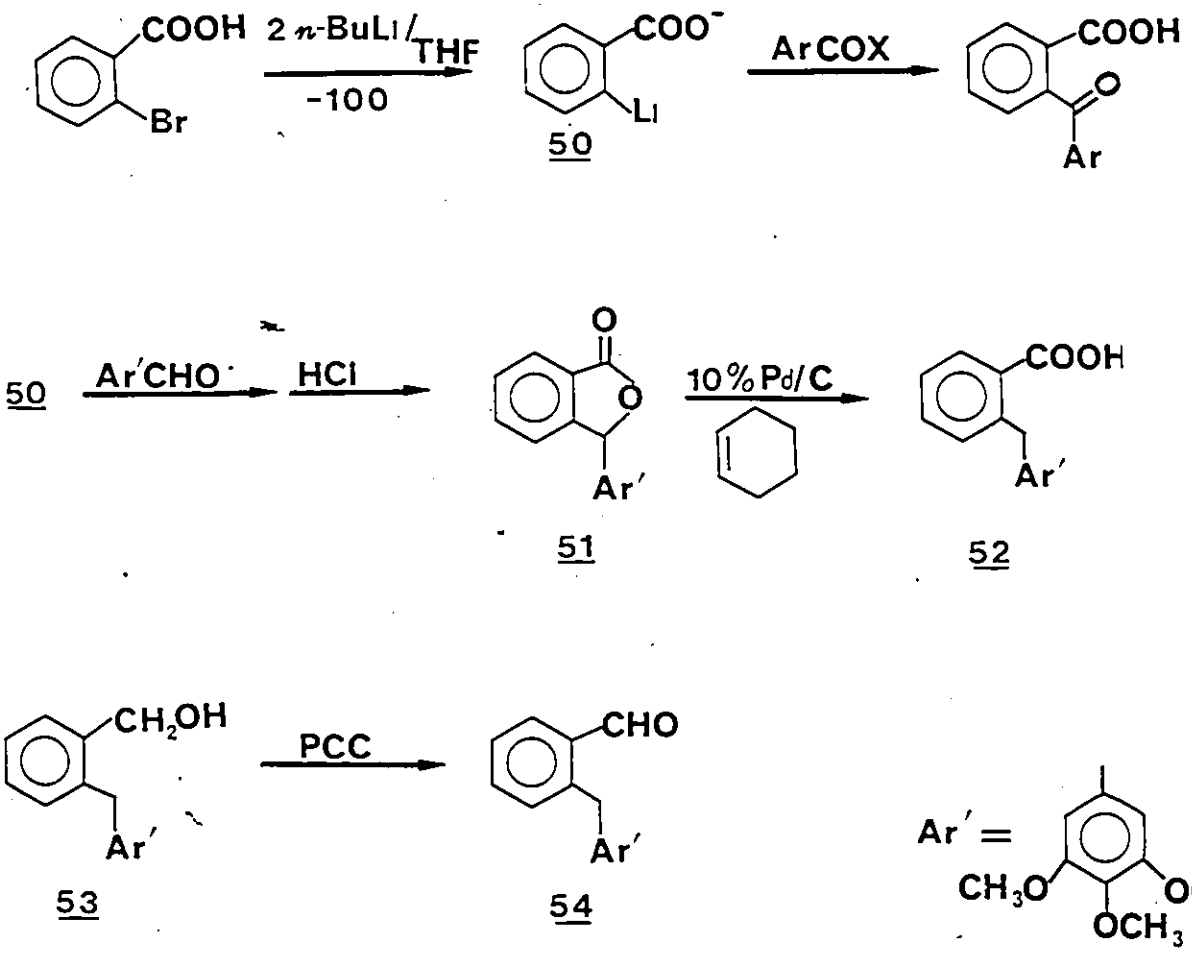


SCHEME 8 GLINSKI'S SYNTHESIS OF ORTHO-SUBSTITUTED BENZALDEHYDES

An earlier synthesis by Sammes [46] of this aldehyde required six steps starting from 6-bromopiperonal ethylene ketal and occurred in 27% overall yield. Thus, an alternate route was investigated as a more reliable and efficient synthesis of these

aldehydes. This route is shown below in Scheme 9.

Parham and coworkers [47] reported that o-bromobenzoic acid could be dimetallated with n-butyllithium in tetrahydrofuran at -100° to give the dianion 50 which when trapped with acyl halides yielded o-benzoylbenzoic acids. If this dianion were quenched with an aldehyde, the key lactone 51 should be formed upon treatment of the initial condensation product with HCl.



SCHEME 9 PROPOSED SYNTHESIS OF ORTHO-SUBSTITUTED BENZALDEHYDES

The dianion 50 was generated according to Parham and reacted with 3,4,5-trimethoxybenzaldehyde. The crude addition product was quenched with 6N HCl and allowed to warm to room temperature. Workup followed by recrystallization from ether/hexanes afforded the lactone 51 as a white solid (mp 125 - 127°) in 64% yield. This reaction was repeated several times including a twelve gram batch, all with comparable yields.

The 300 MHz proton NMR spectrum of 51, shown in Figure 1, shows singlets at δ = 3.84 (6H, 2 $-OCH_3$), 3.86 (3H, $-OCH_3$), 6.35 (1H, -CHO-), 6.48 (2H, aromatic H's on trimethoxy ring); the remaining 4 H's on the disubstituted ring appear as two doublets and two triplets. The individual assignments are shown on Figure 1. The IR spectrum showed a carbonyl absorption at 1740 cm^{-1}, indicative of a conjugated five membered lactone. The mass spectrum gave a strong molecular ion at m/e 300 (calculated M+ = 300). The initial loss of CO_2 to m/e 256 is as expected.

The next step was the conversion of the lactone to the o-benzylbenzoic acid 52. We chose to utilize a process known as catalytic transfer hydrogenation [48] in which an organic molecule acts as the hydrogen donor (e.g. cyclohexene) in the presence of a catalyst (e.g. Pd/C). The process has been utilized

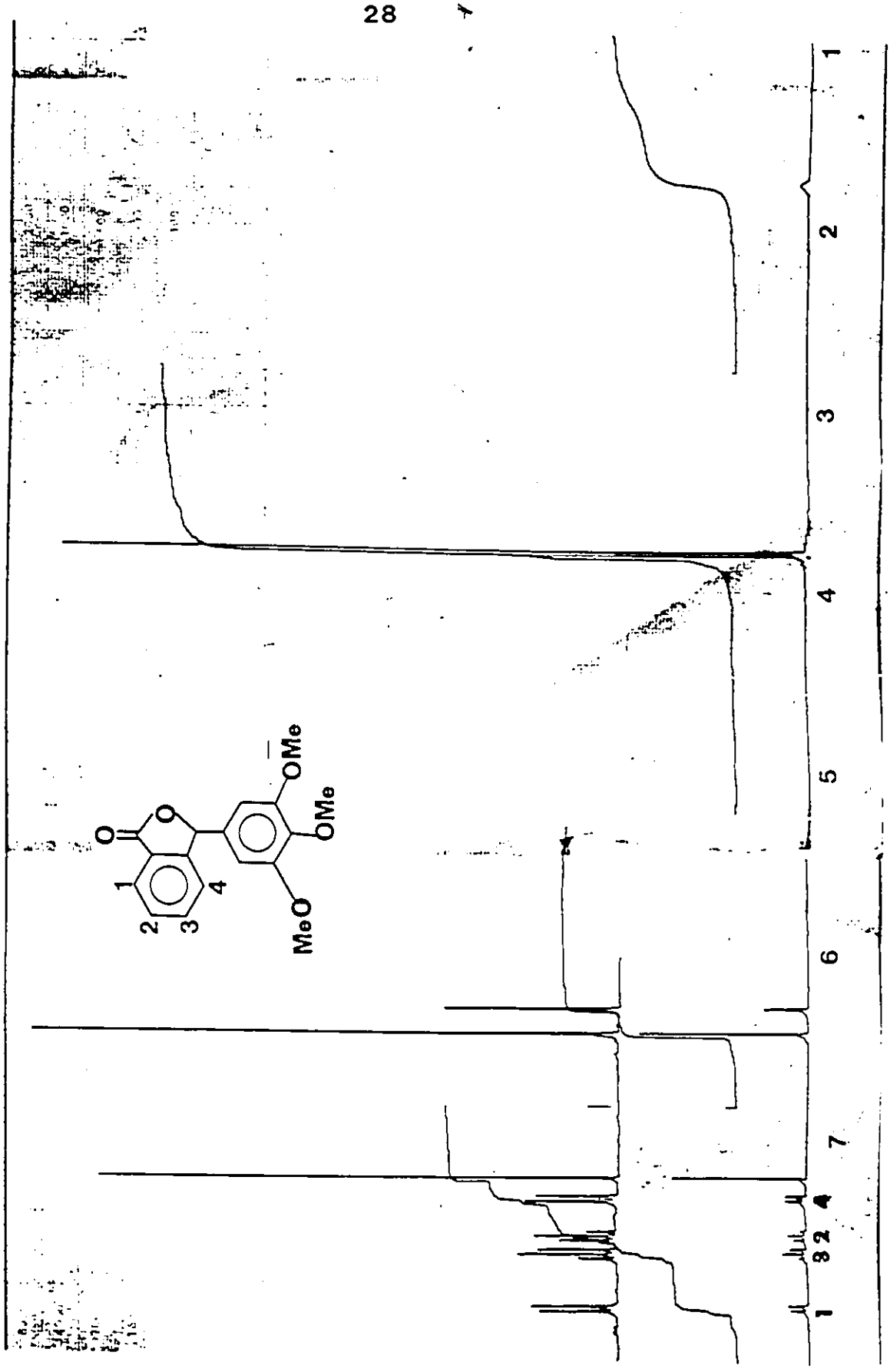


FIGURE 1 ^{1}H NMR SPECTRUM OF THE LACTONE 51

successfully for the hydrogenation of a variety of functional groups including ketones, nitriles, and nitro compounds, and for the hydrogenolysis of benzylic halides, amines, and esters.

The lactone 51 was then refluxed in toluene in the presence of 10% palladium on charcoal and excess cyclohexene for 22 hours. The catalyst was removed by filtration and the solvent evaporated to give the acid 52 as colourless crystals in quantitative yield. The IR showed absorptions at 1705 cm^{-1} (s) and 3290 cm^{-1} (br). The mass spectrum gave a molecular ion at m/e of 302 (calculated M^+ of m/e 302). The proton NMR showed singlets at δ = 3.83 (6H, 2 $-OCH_3$), 3.85 (2H, $-OCH_3$), 4.39 (2H, benzylic CH_2), 6.41 (2H, aromatic H's on trimethoxy ring); the four H's of the B ring appear in the region 7.23 to 8.27 as two doublets and two triplets.

The acid was reduced with lithium aluminum hydride in tetrahydrofuran to give the alcohol 53 in 91% yield. This alcohol was characterized by its proton NMR (δ = 3.83 (6H), 3.85 (3H), 4.35 (2H), 4.63 (2H), 6.40 (2H), and 7.21 - 7.99 (4H)), its IR (3650 cm^{-1}), and its M.S. (M^+ = 288 m/e).

Two methods were utilized to oxidize the alcohol to the aldehyde 54 with similar results. Both pyridinium chlorochromate

(PCC) and manganese dioxide were used as oxidizing reagents and gave 54 in 93% and 94% respectively. PCC is, however, the reagent of choice since rather large quantities of MnO_2 and long reaction times are required to complete the oxidation and the activity of the catalyst decreased greatly with its age. The aldehyde, isolated as a white powder, mp 143.5-146.0°, gave a molecular ion at m/e 286 in its M.S. The IR spectrum displayed a carbonyl absorption at 1698 cm^{-1} indicating the presence of a conjugated carbonyl group. The proton NMR spectrum, reproduced in Figure 2, shows singlets at δ = 3.83 (6H, 2 $-OCH_3$), 3.86 (2H, $-OCH_3$), 4.37 (2H, benzylic CH_2), 6.40 (2H, aromatic H's on trimethoxy ring), and a singlet at δ = 9.2 due to the aldehydic proton. The aromatic hydrogens are between δ = 7.23 - 8.00.

This method provides an efficient method of synthesizing the o-benzylbenzaldehyde 54 from o-bromobenzoic acid with an overall yield of 54% in only four steps. Although each intermediate was purified at each step no purification is actually necessary. The crude lactone obtained from the dianion reaction can be hydrogenolyzed and the acid formed separated from impurities by a simple acid-base extraction, reduced, and the alcohol thus produced oxidized to 54. When such an operation was carried out,

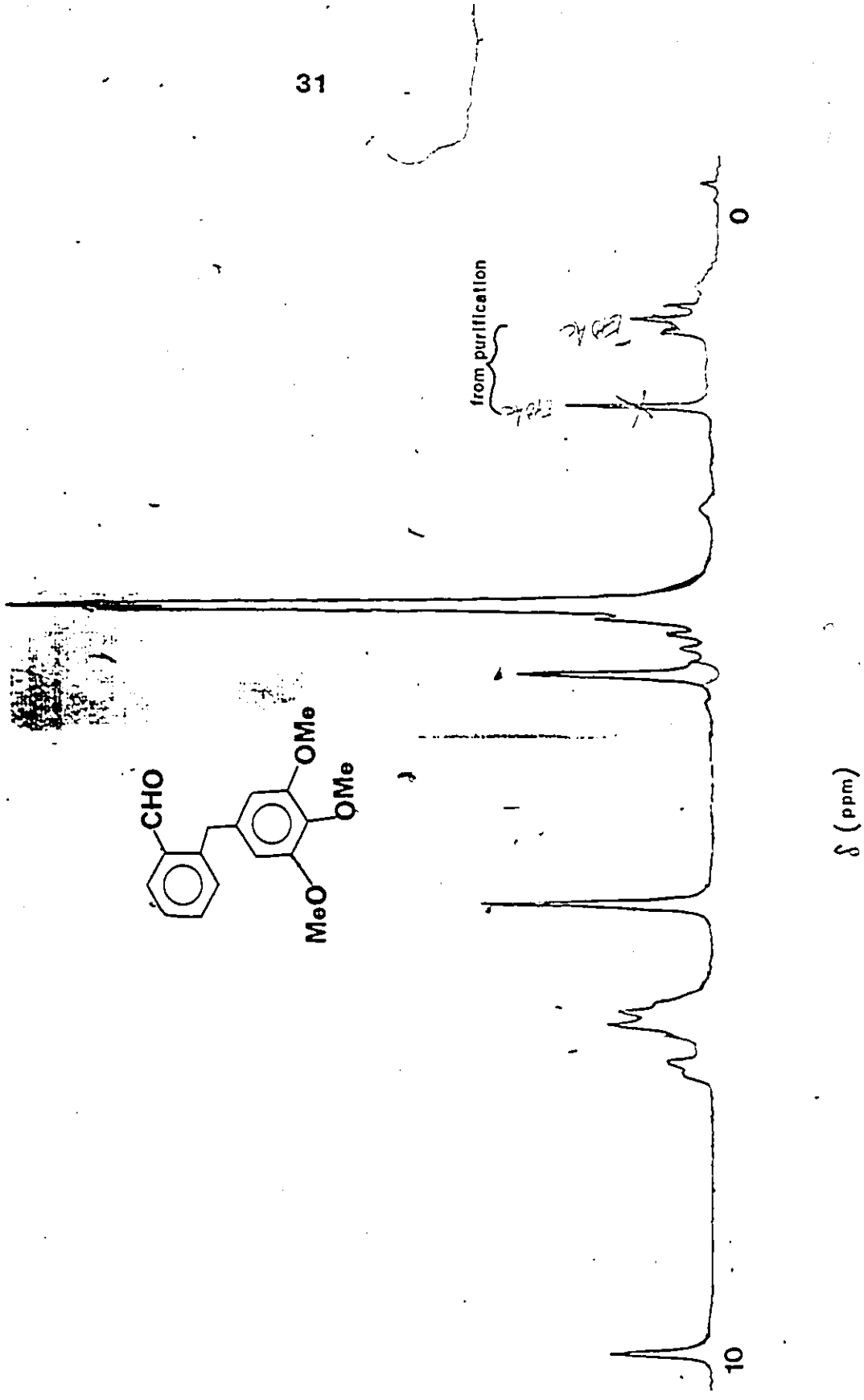


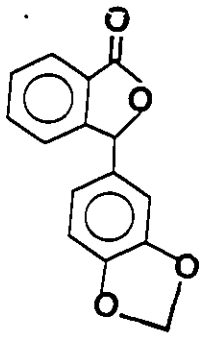
FIGURE 2 ^{1}H NMR SPECTRUM OF THE ALDEHYDE 54

the yield of the aldehyde 54 from o-bromobenzoic acid was 60%.

To demonstrate the generality of the above method for preparing o-benzylbenzaldehydes, the lactones 55 and 56 were prepared, the latter by L. Breau.[64] Both were subsequently hydrogenated to their respective acids 57 and 58. The latter acid could serve as a precursor to the Glinski aldehyde 74 (Scheme 8, page 25) subsequently used in her synthesis of epiisopodophyllotoxin.[44]

The dianion of o-bromobenzoic acid was again generated as described above. Addition of piperonal and quenching of the reaction mixture with 6N HCl yielded, after recrystallization from ether/hexanes, the lactone 55 as a white solid in 62% yield. The IR showed the expected carbonyl absorption at 1735 cm^{-1}. The mass spectrum gave a molecular ion at m/e of 254 (calculated M^+ of m/e of 254). The ^1H NMR shows signals at δ = 5.94 (s,2H), 6.34 (s, 1H), 6.45 -6.68 (m, 3H), 7.10-7.25 (m, 2H), 7.39-7.42 (m, 1H), and 7.98 - 8.01 (d, 1H).

The lactone 55 was refluxed in toluene along with excess cyclohexene and 10% palladium on charcoal as was earlier described. Workup furnished the acid 57 (99%) as white prisms. It was characterized by its M.S. (M^+ = 256), IR (3650 cm^{-1}), and ^1H



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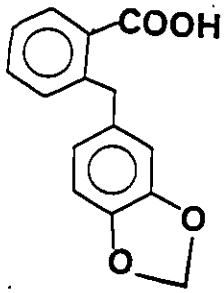

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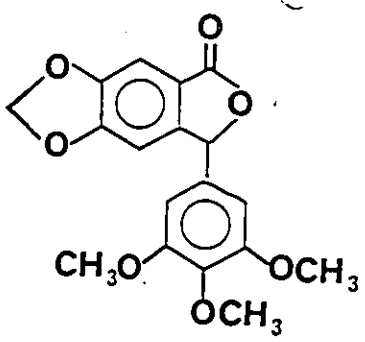
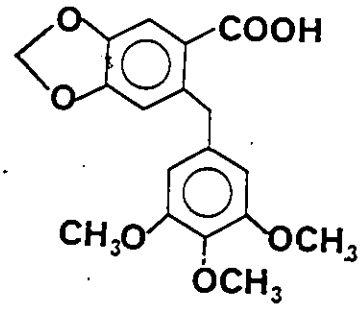


56



58

NMR (δ = 4.36 (s, 2H), 5.98 (s, 2H), 6.48 - 6.70 (m, 3H), 7.16-7.30 (m, 2H), 7.40 - 7.46 (m, 1H), and 7.98 - 8.02 (d, 1H)).

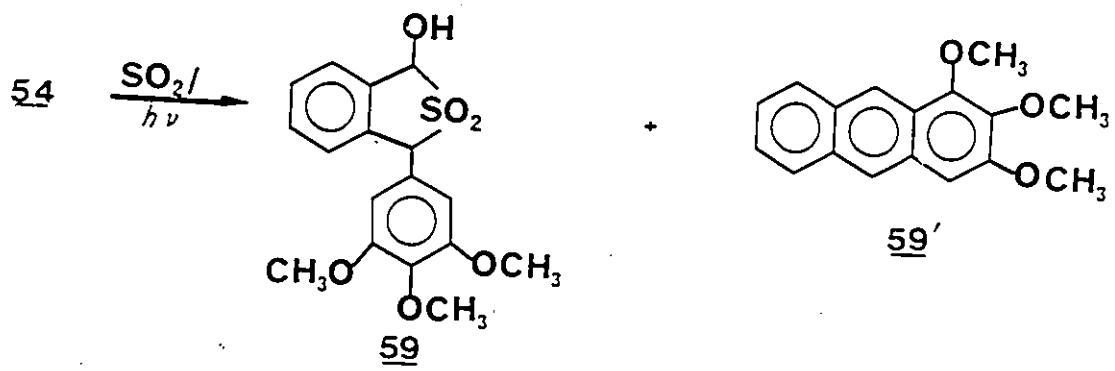
The next step in the synthesis of 49 was the preparation of the hydroxy sulfone 59. The method utilized was based on work by Durst and Charlton.[49]

The first major hurdle was encountered at this stage. 2-(3', 4',5'-Trimethoxybenzyl)-benzaldehyde was photolyzed in the presence of sulfur dioxide. After 3 hours, the TLC indicated the absence of aldehyde and the formation of a slower moving compound presumed to be the sulfone. Also visible on the TLC was a fast moving fluorescent material. The benzene was evaporated and the resulting oil was washed several times with hexane. After much effort the sulfone was isolated in 55% yield as a 2:1 mixture of diastereomers as supported by the spectroscopic data. The diastereomers were not separated. Isomer 1 displayed signals at δ = 3.78 (s, 3H), 3.80 (s, 6H), 5.32 (s, 1H), 5.72 (s, 1H), and 7.20-7.98 (m, 4H). Isomer 2 gave signals at δ = 3.79 (s, 3H), 3.83 (s, 6H), 5.47 (s,1H), 5.68 (s, 1H), and 7.19 - 7.98 (m, 4H). The IR spectrum of the mixture displayed bands at 3500 cm^{-1}, 1530 cm^{-1}, and at 1310 cm^{-1}. The mass spectrum did not give a molecular ion but showed an m/e of 288 ($M^+ - SO_2$) as its base

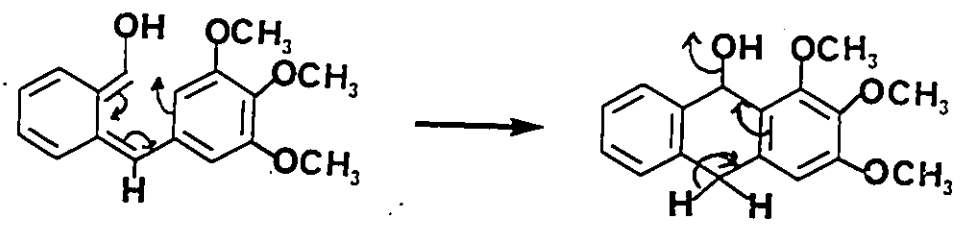
peak. The facile loss of sulfur dioxide from the molecular ion peak was not unexpected as Macdonald observed similar results with his sulfones.[41]

The sulfone 59 was found to be very unstable. Gentle heating or in fact merely sitting at room temperature would cause its decomposition. The sulfone was also very insoluble in most solvents.

The fluorescent byproduct obtained in the photolysis of 54 was isolated in 29% yield and characterized as the trimethoxy anthracene derivative 59 shown below by its NMR (δ = 4.02 (s, 3H), 4.06 (s, 3H), 4.52 (s, 3H), 7.44-7.47 (br, 2H), 7.88-8.21 (m, 3H), 8.64 (s, 1H), and 8.68 (s, 1H)), and its M.S. (m/e of 268). A proposed mechanism for its formation is shown below.

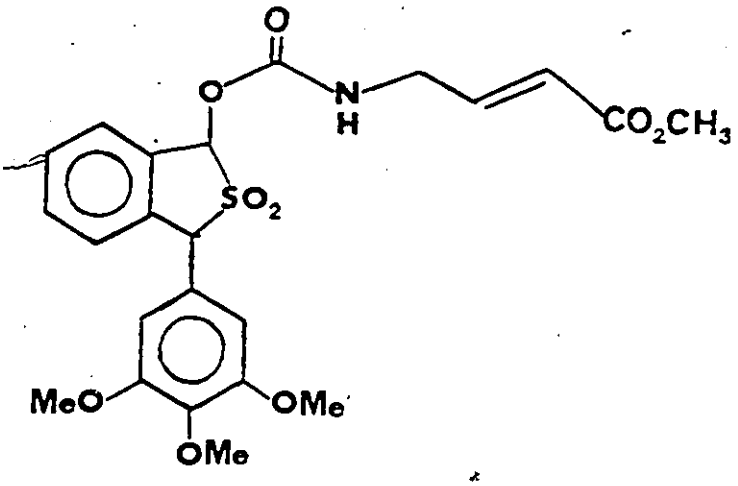


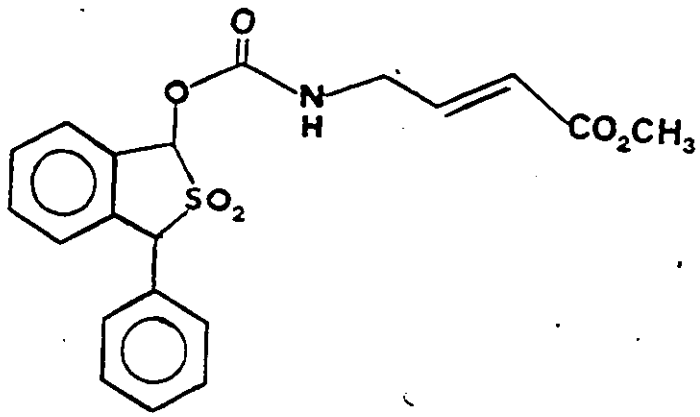
MECHANISM (59′):



Based on earlier studies in our laboratory by D. Macdonald, we expected that the coupling reaction between the isocyanate 60 and the sulfone 59 would proceed without much difficulty. In an intial attempt 10 mole % of triphenyltin acetate was added to a suspension of the sulfone in methylene chloride. After several hours the methylene chloride was removed at 25° to furnish a viscous oil. An IR spectrum of the oil showed a strong peak at 2230 cm^{-1} indicating the presence of isocyanate. Thus methylene chloride was added to the reaction flask and the suspension was kept at room temperature for several hours at which time the solvent was again evaporated. This process of evaporation and dilution was repeated for several days until the IR had indicated that the starting isocyanate had disappeared. Finally, the crude product was passed through a silica gel column using varying mixtures of hexane and ethyl acetate. Unfortunately, none of the desired material was isolated. Many further attempts were made by varying solvent type (acetonitrile, methylene chloride) and catalyst amounts (from 10 mole % to 2 mole equivalents). In one experiment (1 mole % triphenyltin acetate, methylene chloride, 48h), a compound suspected to be the desired urethane was isolated in 10% yield. This material showed ^1H NMR peaks at δ =

3.72 (s, 3H), 3.76 (s, 3H), 3.81 (s, 6H), 4.02 (m, 2H), 4.91 (m, NH), 5.43 (s, 1H), 5.95 (d, 1H), 6.40 (d, 2H), 6.59 (s, 1H), 6.85 (dt, 1H), and 7.20-7.99 (m, 4H). Comparison of these data with those of the known urethane structure 34' whose individual proton assignments are at δ = 3.73 (s, 3H), 4.07 (m, 2H), 5.17 (m, NH), 5.55 (s, 1H), 6.00 (dt, 1H), 6.67 (s, 1H) 6.92 (dt, 1H), and 7.0 -7.6 (m, 9H) allowed us to draw the above conclusion concerning the identity of our coupling product.



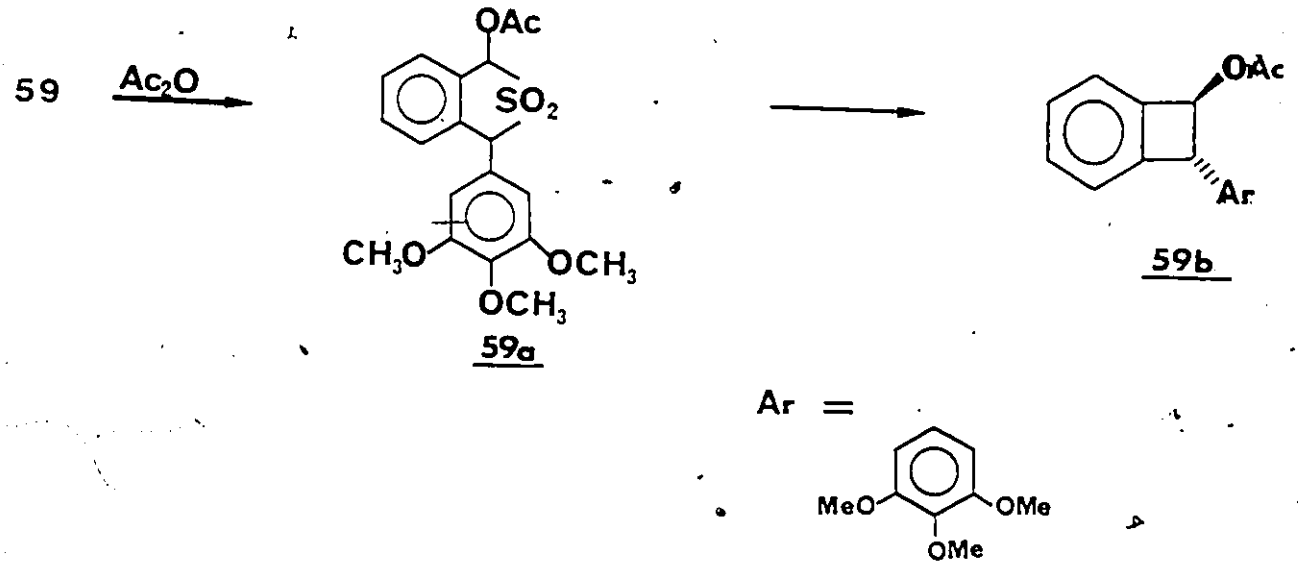


34'

The reason for the poor yield (at best) of the coupling product is probably due to the instability and insolubilty of the

sulfone 59. Because of these two factors the sulfone may have undergone decomposition prior to significant reaction with the isocyanate. In the end the isocyanate itself was probably destroyed by the presence of adventitious water resulting from the many solvent manipulations. A 10% yield at this stage would not be sufficient to allow us to generate sufficient quantities of the desired podophyllotoxin analogue and thus, the approach had to be abandoned.

We then turned to the benzocyclobutenol approach shown in Scheme 7 (page 22). This would involve preparation of the sulfone acetate 59a (Scheme 10) followed by thermolysis to the benzocyclobutyl acetate 59b. A large excess of acetic anhydride was added to the sulfone and the reaction mixture was kept at room temperature for 5 hours. Frequent TLC monitoring indicated the formation of considerable amounts of the anthracene derivative described above. The NMR of the crude reaction mixture obtained after evaporation of the acetic anhydride showed that extensive decomposition had occurred, and gave no evidence for the formation of the desired acetate 59a. At this point, the synthesis of the podophyllotoxin analogues 48 and 49 via the benzothiophene sulfone route was abandoned.



SCHEME 10 SYNTHESIS OF THE ACETATE OF SULFONE ACETATE 59a

PART II

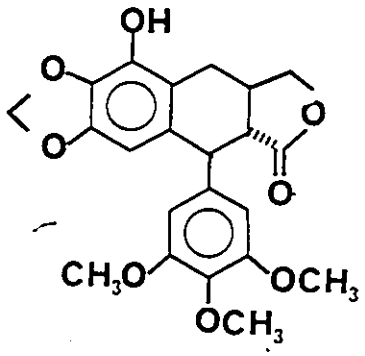
In 1947, Hartwell and workers isolated α -peltatin 7 and β -peltatin 8 from Podophyllum peltatum. [8,9,10] It was initially thought that both peltatins were isomeric to podophyllotoxin 1 [10] but it was later shown that the empirical formula for α -peltatin was $C_{21}H_{20}O_8$ [50] while that of β -peltatin was $C_{22}H_{22}O_8$. [9,10]

The peltatins are known to be biologically very active and highly toxic. [8,9,10,51] A combination of poor response in cancer patients and a high toxicity resulted in these compounds being virtually ignored by researchers after the work of Greenspan in 1950. [11]

At the present time, no total synthesis of either α -peltatin or β -peltatin has been reported. Brown, Loriot, and coworkers have reported a synthesis of (±)-iso- β -peltatin 61 and the methyl ethers of both (±)-iso- α -peltatin 62 and β -peltatin 63. [52,53] A synthesis of β -peltatin starting from podophyllotoxin has also been reported. [54]

At the beginning of this thesis work a project directed towards the synthesis of both α - and β -peltatin was initiated.

The proposed scheme (Scheme 11) shown below is analogous to that Macdonald was simultaneously investigating for the synthesis of podophyllotoxin. (Scheme 6, page 19)



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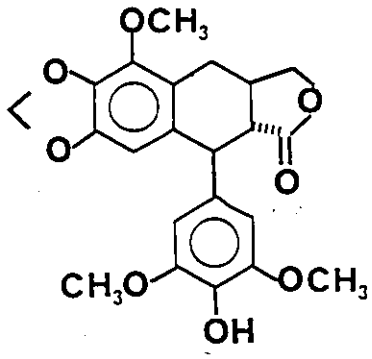

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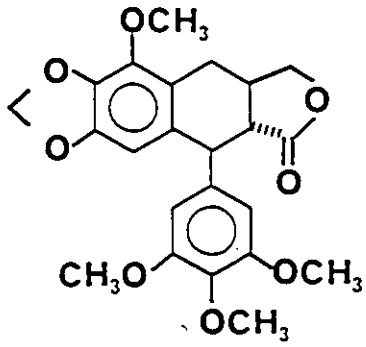
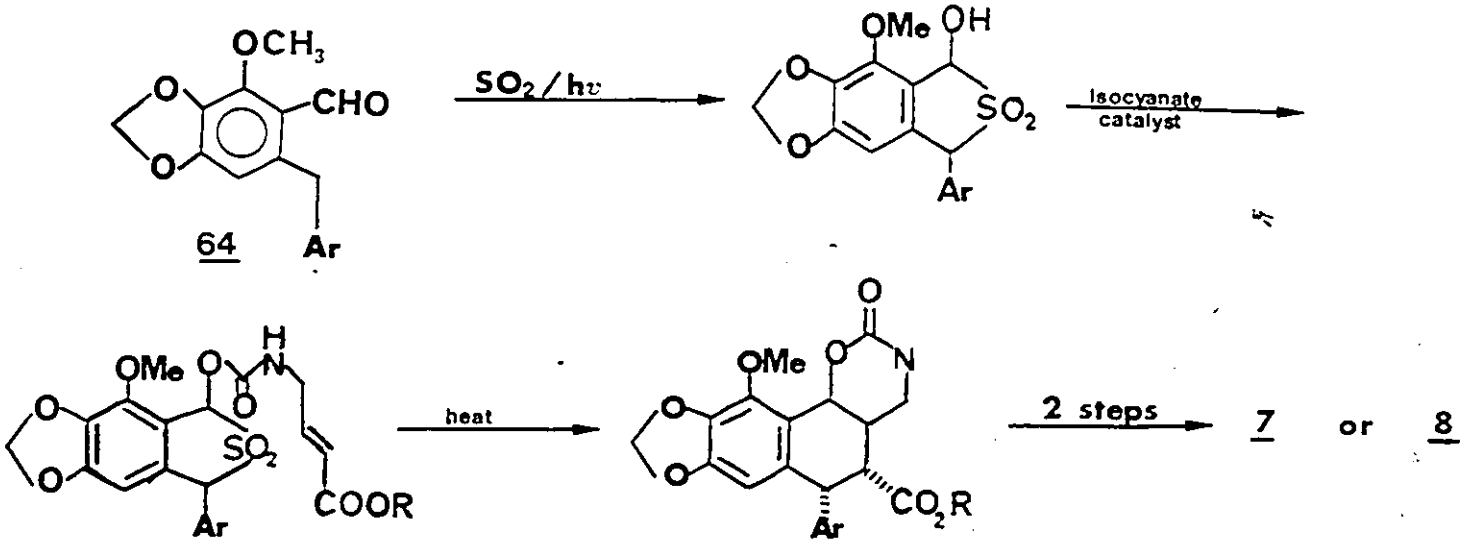
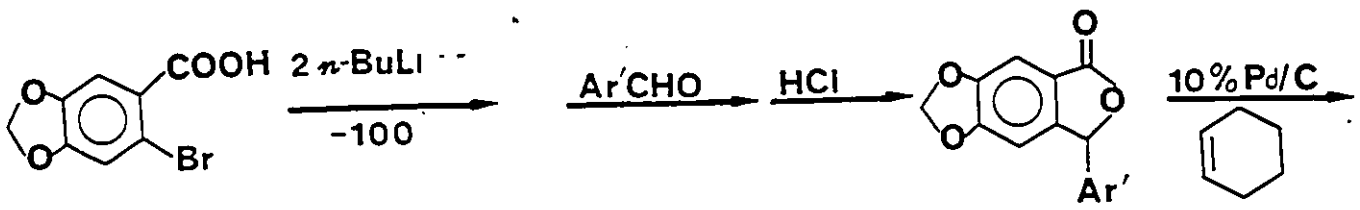


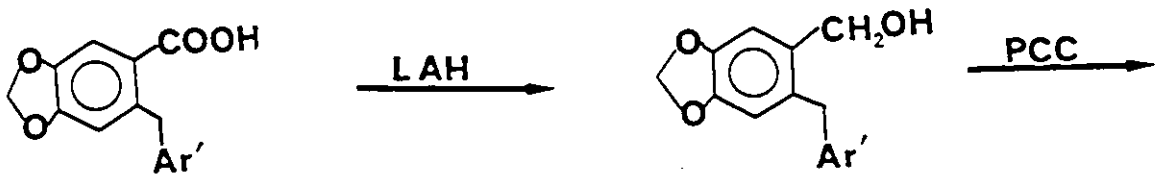
63

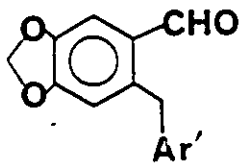


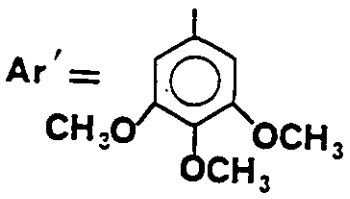
SCHEME 11 PROPOSED ROUTE FOR THE SYNTHESIS OF THE PELTATINS

In order to proceed, a route to the aldehyde 64 was required. In the following pages, an unsuccessful approach to this compound based on the Glinski coupling reaction described earlier and variations thereof is described. Unfortunately, the development of a synthesis of such aldehydes, which is described in Part I, came at a significantly later stage and time did not permit the application of this new methodology to the synthesis of 7 or 8. Based on experience, there appears to be no reason why 64 should not be available via the sequence shown below.



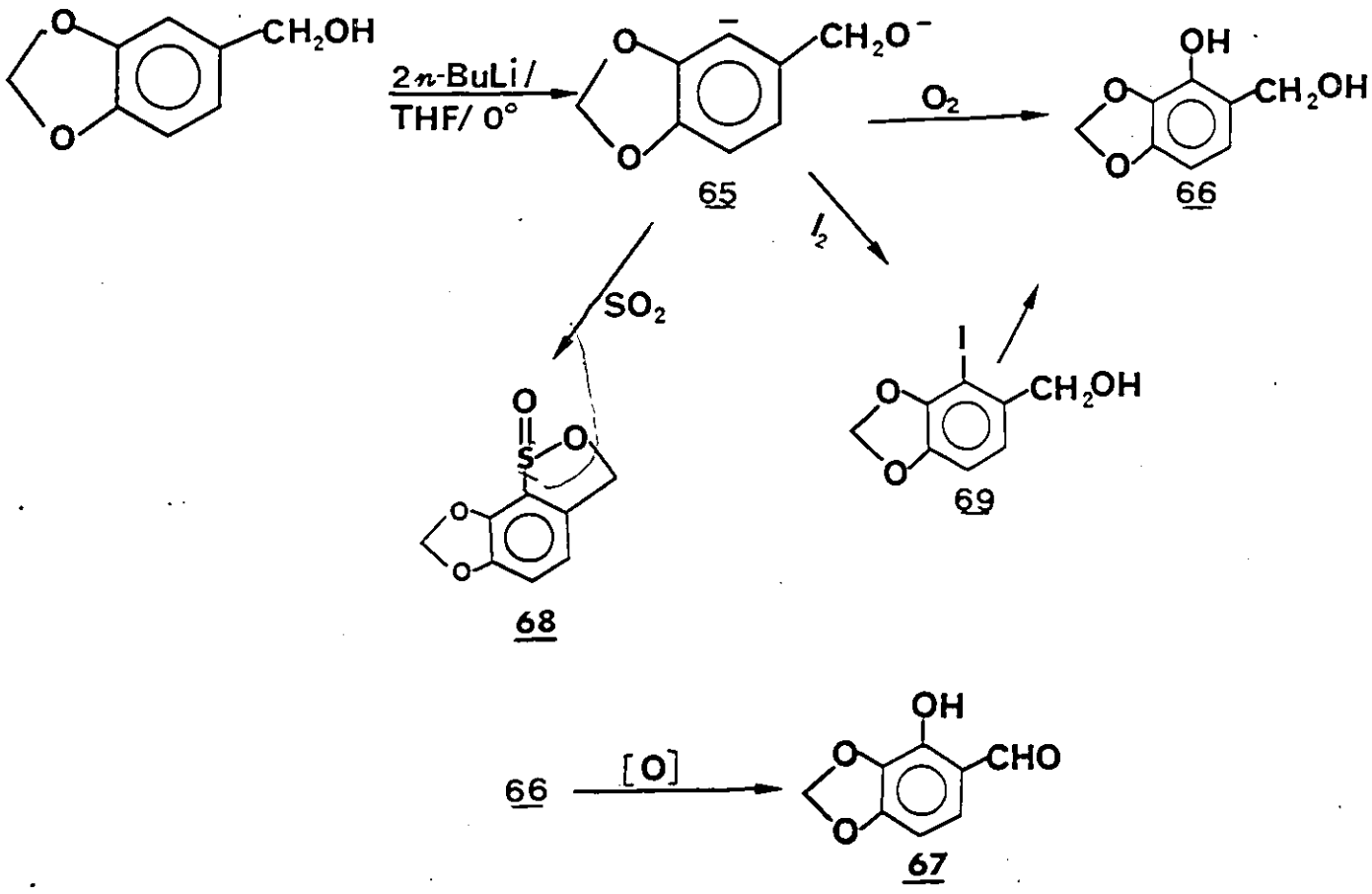






The question of whether 64 could be converted via the hydroxy sulfone to the desired compound remains unanswered in view of the problems associated with dealing with the corresponding sulfone 59 in the podophyllotoxin series.

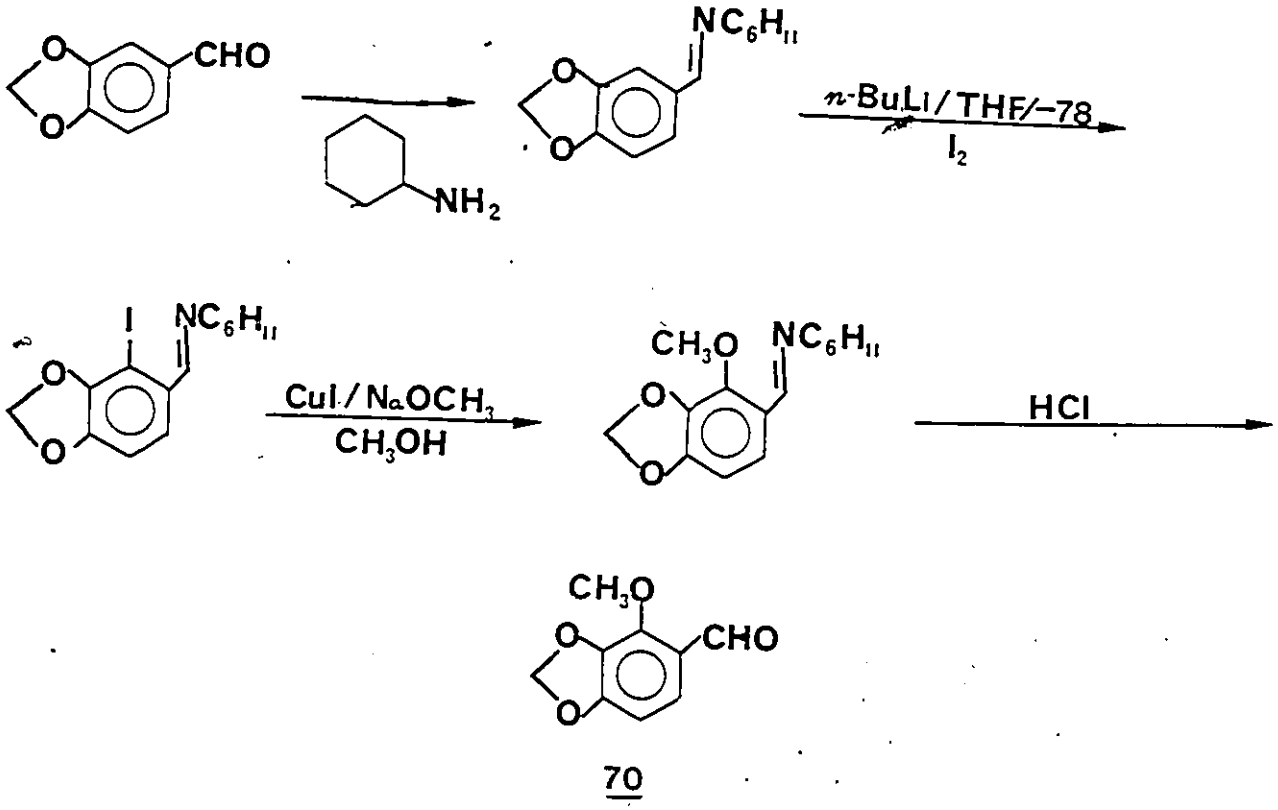
The first stage of the project involved the formation of 2-hydroxy piperonal 67. It was initially thought if the dianion of piperonal 65 could be formed, quenching with oxygen would provide a simple route to the aldehyde 67 as shown below. The dianion 65 was previously prepared by Durst and workers and subsequently trapped with SO_2 to give the sultine 68. [55]



Piperonol, dissolved in dry THF, was cooled to 0°. Two equivalents of n-BuLi were added slowly. After two hours, oxygen was bubbled directly into the reaction mixture. Examination of the crude reaction mixture by NMR and TLC indicated the presence of a complicated mixture. None of the desired phenol could be isolated from the crude reaction mixture either by chromatography or after attempted separation of the reaction mixture into acidic and non-acidic components by extraction with 10% KOH solution. This reaction was repeated several times by varying the temperature for dianion reaction with oxygen from -78° to 0° and the reaction solvent from THF to ether.

A subsequent approach involved reaction of the dianion 65 with I_2 as shown below. The expected iodide 69 could eventually be converted to the required phenol. Unfortunately, treatment of 65 with one equivalent of I_2 at 0° followed by warming the reaction mixture to room temperature and subsequent treatment with Na_2SO_3 did not afford the desired product. Several modifications concerning reaction times, temperature, and solvent also proved unsuccessful.

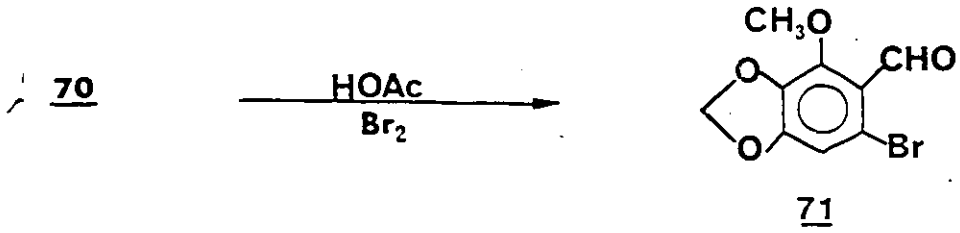
Adesomoju and coworkers [56] have reported the preparation of 2-methoxypiperonal 70, a compound potentially useful for the peltatin synthesis. This synthesis, shown in the sequence below, was successfully repeated. The overall yield of 2-methoxypiperonal 70 from piperonal via its cylclohexylimine as an ortho metallating group, was a useful 55%. [56,57] The physical and spectral properties of 70 and all intermediates were in agreement with the literature values.



70

Reaction of 70 with bromine in glacial acetic acid [58] gave 6-bromo-2-methoxypiperonal 71, mp 138.2 - 139.8, (λ_{max} = 1690

cm^{-1}) as a white solid in 75% yield. The 300 MHz proton NMR showed singlets at δ = 3.97(3H, $-OCH_3$), 5.95 (2H, $-OCH_2O-$), 6.82 (1H, aromatic H), and 10.48 (1H, CHO). The presence of a molecular ion "doublet" at m/e 258 and m/e 260 confirmed the presence of bromine.

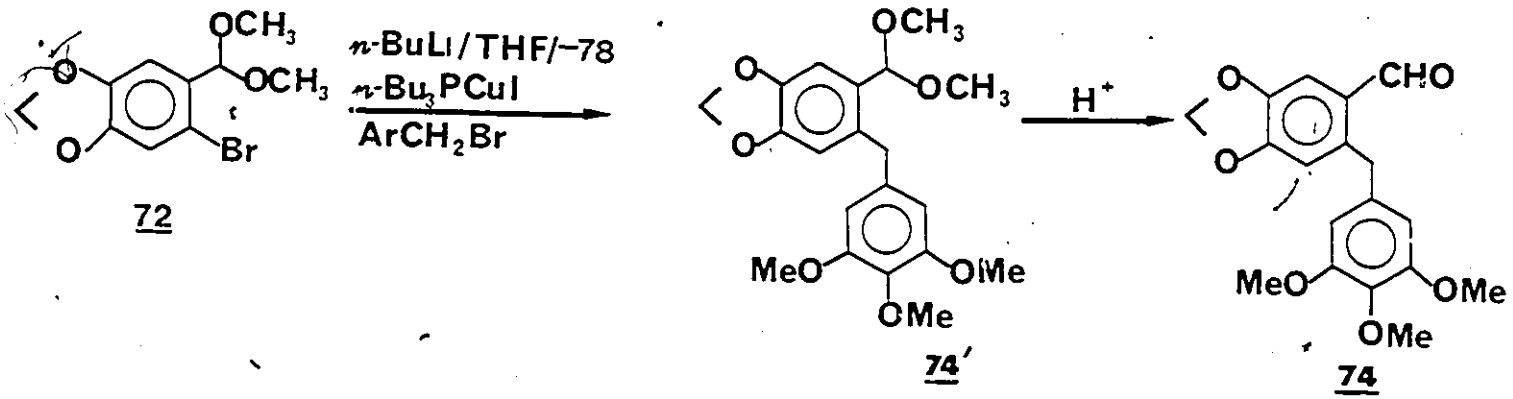


71

The bromo derivative 71 is now susceptible to halogen-metal exchanges which would allow us to join the second aryl group to ring B. The goal of this part of the project was to devise a reliable method of attaching the aryl group. For these studies, 6-bromopiperonal and 3,4,5-trimethoxybenzene derivatives were chosen as model components because of their ready availability.

The Glinski coupling reaction discussed earlier was first explored as described. [44,45] Particular care was taken to ensure the purity of all starting materials. They were carefully

recrystallized and dried prior to use. A solution of 6-bromopiperonal dimethyl acetal 72 in dry THF was treated with nBuLi at -78°. This was followed by the addition of $(nBu)_3PCuI$ and then 3,4,5-trimethoxybenzyl bromide. The reaction mixture was then warmed to room temperature and stirred for 18 hours. However, none of the coupled product 74' was isolated upon workup and column chromatography.

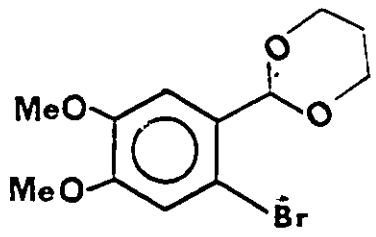


72 74' 74

Many additional attempts were made in order to match the Glinski result. These included the addition of TMEDA to the reaction mixture with the hope of stabilizing the intermediate aryl anion and possibly improve the coupling reaction. Under the best conditions(TMEDA,$(nBu)_3PCuI$,nBuLi (-78°,10min), 3,4,5-trimethoxybenzyl bromide (-78°, 5 min.), warm to RT) an approximately 31% yield of 74' was obtained after extensive chromatographic separation. We decided to abandon this approach because of the

inconsistency of the results obtained from the experiments.

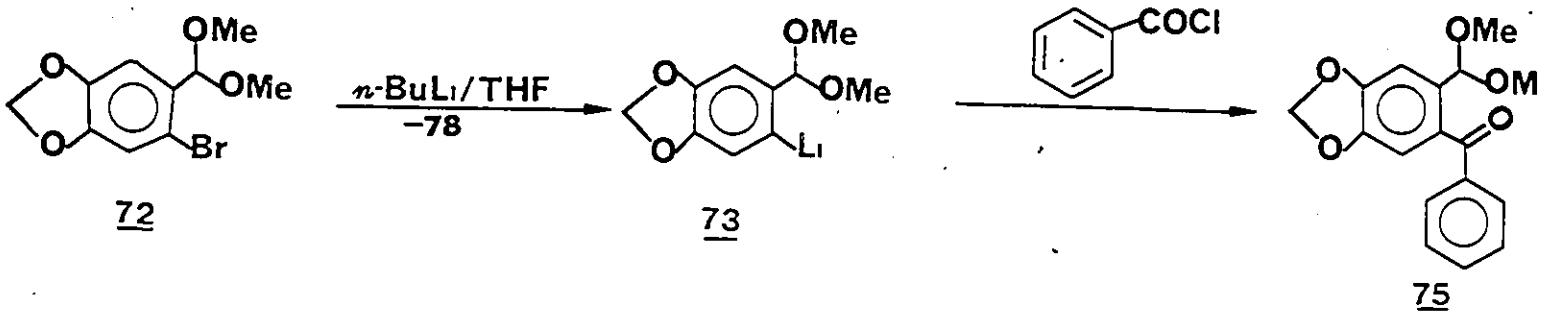
Several months later, Charlton also attempted the Glinski coupling reaction on 74a and also experienced many difficulties. [59] During the course of his studies several conclusions were made. He found that the purity of the benzyl bromide was most crucial. Also, the aryl anion 73 had to be reacted with the benzylic bromide almost immediately after its formation. This information came at such a later date that due to lack of time and other committments, his reaction condition was not attempted with our compounds.



74a

Since the coupling reaction was unsuccessful, the two step variation shown below was investigated.

Reaction of 6-lithio piperonal dimethyl acetal 73 with benzoyl chloride first at -78° and then at 25° did not afford the expec-

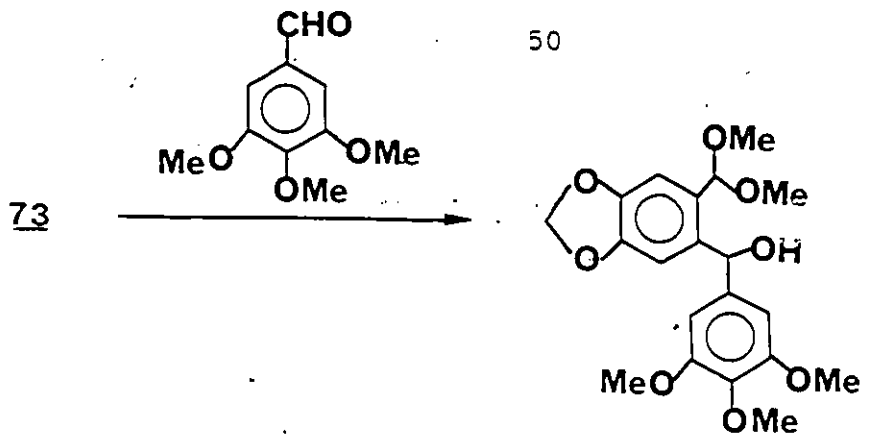


72 73 75

ted benzophenone 75. Examination of the NMR before and after attempted purification indicated none of the desired product had been formed. There was also evidence that only 10% of the starting material was present and that extensive decomposition had also occurred. Presumably, the same instability of the aryl anion as suggested by Charlton is responsible for this negative result.

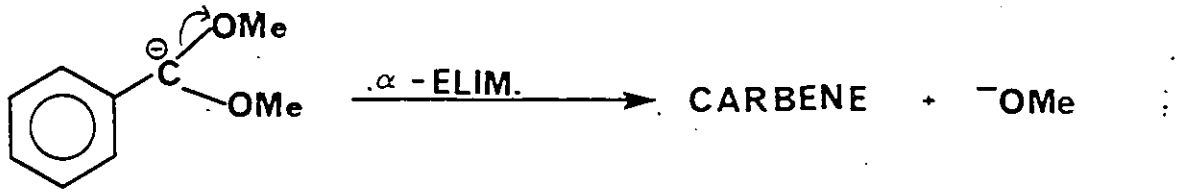
One final attempt was made involving the formation of the anion 73 as shown in the scheme below. The anion was generated as described earlier. One equivalent of 3,4,5-trimethoxy benzaldehyde was added. After normal workup, the NMR of the crude product was quite complicated. Column chromatography of the crude oil gave no product resembling the desired alcohol 76. This result could also point to the instability of the aryl anion.

Based on the above results which were obtained prior to the



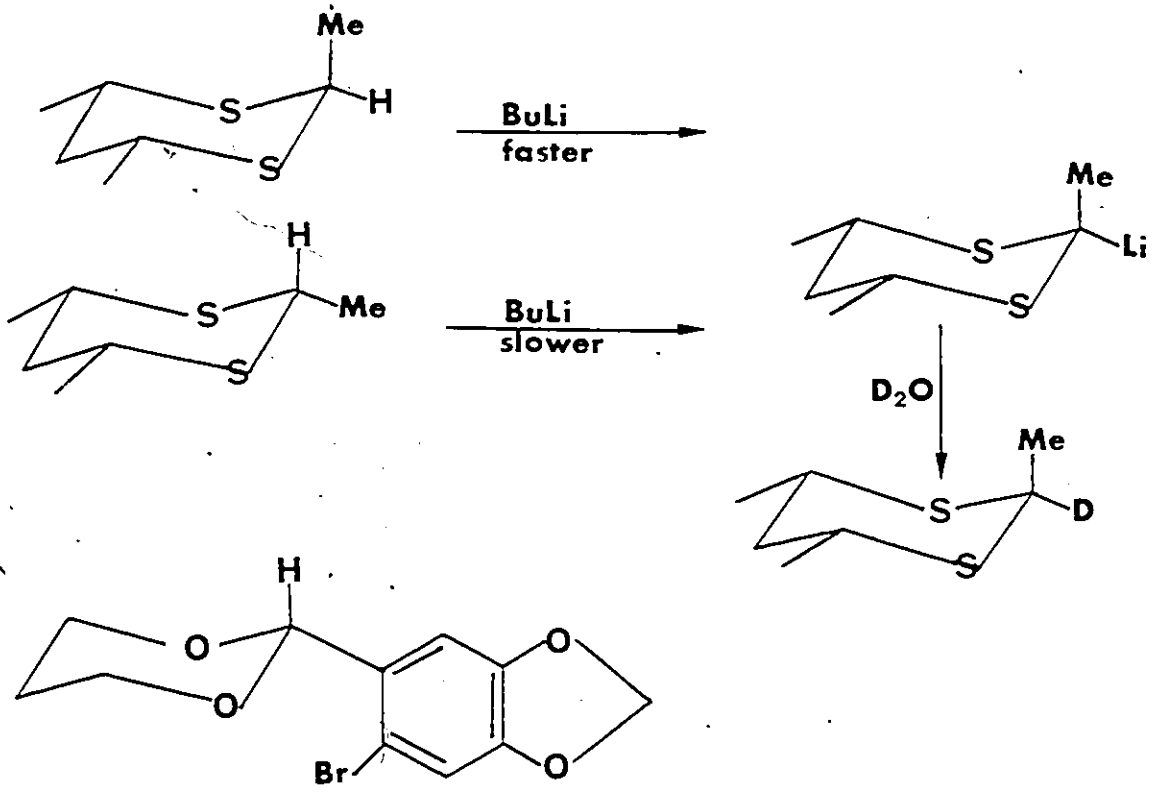
73 → 76

communication with Charlton, it was postulated that perhaps the failure of these reactions was due to the instability of 6-lithiopiperonal dimethyl acetal, possibly by rearrangement to the acetal anion a and subsequent decomposition.



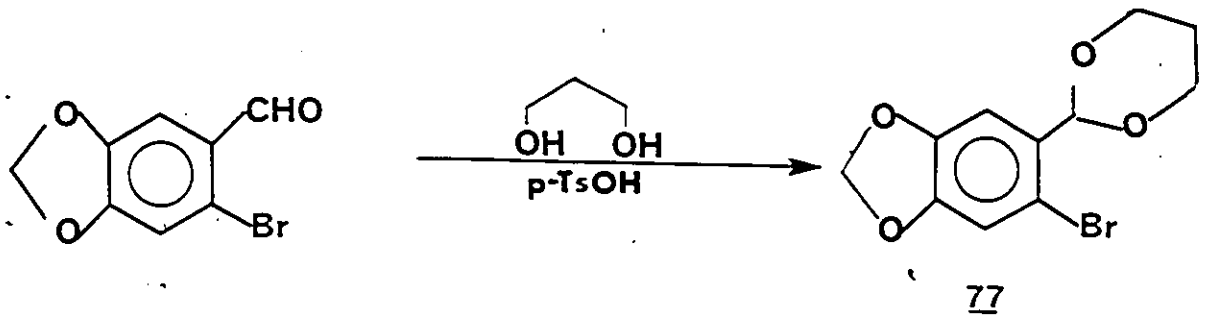
Based on work by Eliel [60], we decided to make the 1,3 dioxane derivative of 6-bromopiperonal 77. Eliel studied lithiation reactions of conformationally fixed 1,3 dithianes. He found that deuteration of 2-lithio-2-methyl-cis-4,6-dimethyl 1,3 dithiane involved equatorial attack by deuterium. He also concluded the lithium salt was formed more rapidly when the 2-methyl

group is axial (i.e. an equatorial hydrogen is more readily abstracted). Based on his results on the dithianes, we rationalized that the benzylic hydrogen of the dimethyl acetal might be more susceptible to lithiation than the same hydrogen in 77. This would cause the instabilty we encountered. However, in 77 the preferred conformation places the benzylic hydrogen in the less acidic axial position which might make it less susceptible to exchange with ortho-aryl lithium species.



77

The 1,3 dioxane derivative of 6-bromopiperonal 77 was prepared by refluxing piperonal with trimethylene glycol and a catalytic amount of p-toluenesulfonic acid. Workup gave the desired ketal as white needles (mp 110-112°) in 88% yield. The acetal hydrogen was found as a singlet at δ = 6.00 in the NMR; the other peaks are as expected and are listed in the experimental section.

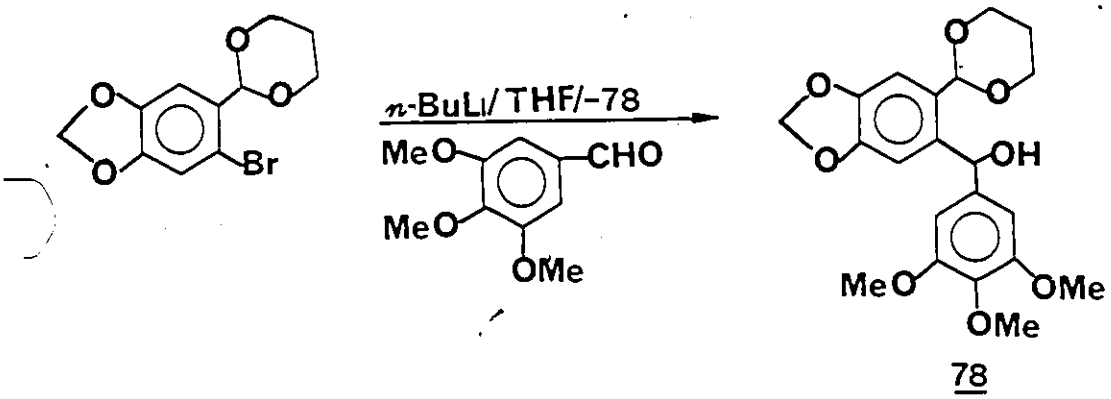


77

The Glinski coupling reaction was again repeated on 77 using similar conditions as described earlier. Again, only unacceptable low yields of the expected coupling product could be attained.

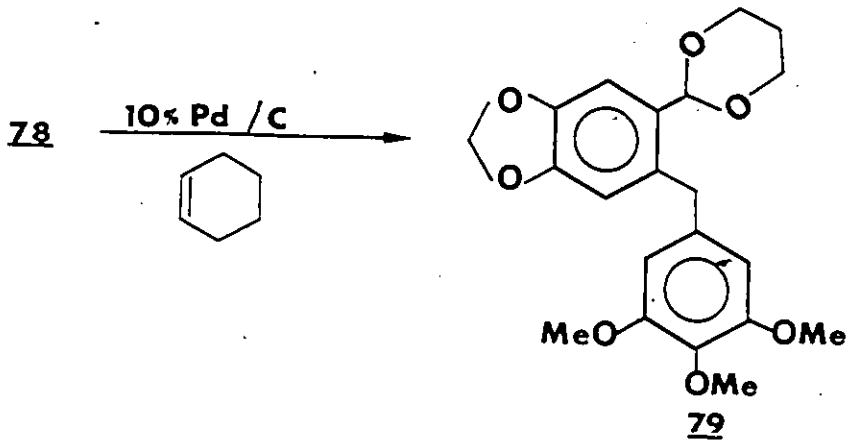
The halogen-metal exchange reaction attempted earlier to yield the alcohol 76 was repeated on the acetal 77 and the anion was reacted with 3,4,5-trimethoxybenzaldehyde. Column chromatography of the crude product afforded the alcohol 78 in 68% yield. The IR spectrum gave an absorption at 3650 cm^{-1}. The 300 MHz proton NMR gave signals at δ = 3.81 (s, 3H), 3.82 (s, 6H), 6.01 (s, 1H),

6.14 (s,2H), 6.38 (s,2H), 6.48 (s, 1H), 7.10 (s, 1H), and 7.21 (s,1H). This result allows one to conclude that the anion exchange reaction has worked but that the coupling with the benzylic halide is poor.

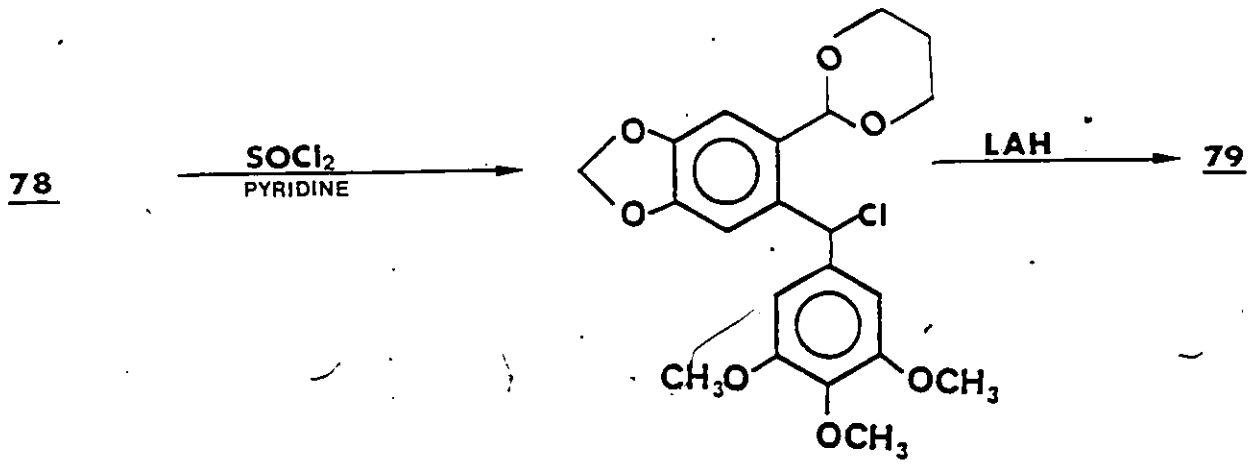


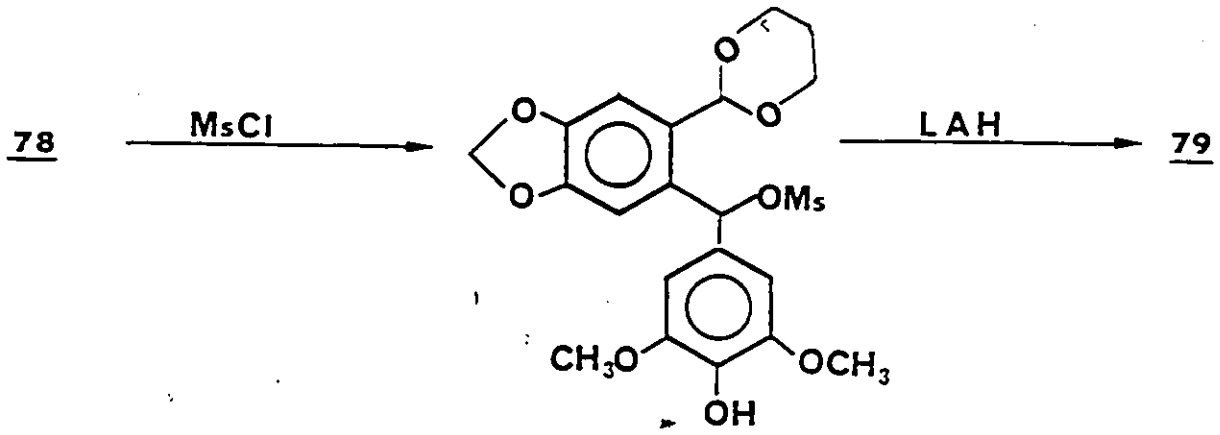
78

The hydrogenolysis of 78 to 79 was attempted using cyclohexene and palladium on charcoal in refluxing toluene. The progress was monitored by TLC. After disappearance of the starting material, the catalyst was removed by filtration and the toluene evaporated. Examination of the product by NMR showed almost the complete absence of any aromatic hydrogens suggesting that hydrogenation of the aromatic ring had taken place. A similar result was subsequently obtained by W. Brown [63] with a related compound. No explanation for this surprising result can be offered.

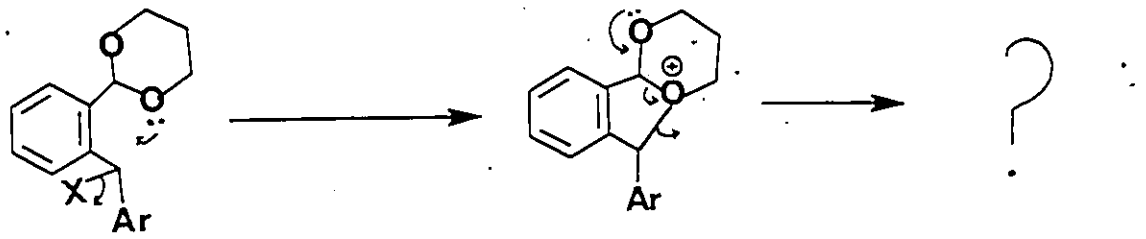


In subsequent attempts, the alcohol was initially converted into either a chloride ($SOCl_2$, pyridine) or a mesylate (mesyl chloride, triethylamine) at low temperature. The product of each was reaction was not isolated and reduced directly with LAH since we expected these compounds to have limited stability. Neither of these conditions afforded 79 but the TLC and ^1H NMR indicated that decomposition had perhaps occurred.



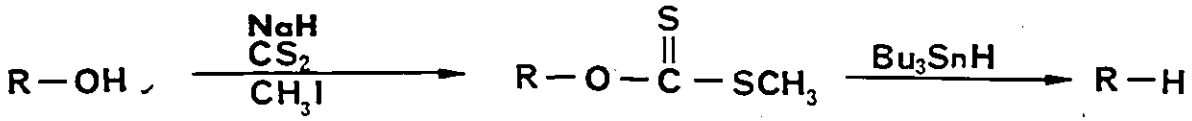


The failure of these sequences may be due to the susceptibilty of the chloride or mesylate toward solvolysis with participation of the dioxolane oxygens followed by further reaction of the resultant tricyclic oxonium anion.



The Barton-McCombie reaction [61,62], a method for the radical deoxygenation of alcohols, was next employed for the attempted conversion of 78 to 79. This method, as shown below, involves the initial formation of an xanthate by addition of carbon disulfide and then methyl iodide to the oxygen anion. Subsequent reduction

with tributyltin hydride results in the deoxygenated derivative.



The alcohol 78 was added to a suspension of sodium hydride and imidazole in THF. The mixture was brought to reflux. Carbon disulfide and CH_3I were added sequentially and the resultant solution was refluxed for two hours. The reaction mixture was washed with water and the solvent evaporated yielding a brownish oil which showed a singlet at δ = 2.68 assignable to the S-Me of the desired xanthate. A solution of the crude product in toluene was added to a refluxing solution of tributyltin hydride in toluene. Evaporation of the solvent after several hours at reflux yielded an oil. The NMR of this crude oil indicated that none of the desired product had formed.

These approaches to the aldehyde 74 were abandoned at this stage.

EXPERIMENTAL

GENERAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian XL 300 MHz spectrometer. All spectra were taken using deuterochloroform ($CDCl_3$) as solvent (unless otherwise indicated) and tetramethylsilane as the internal standard (TMS). The chemical shifts given are relative to the TMS. The coupling patterns are given as singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), broadened (br), or multiplet (m). Mass spectra (EI) were obtained on a VG-7070E instrument.

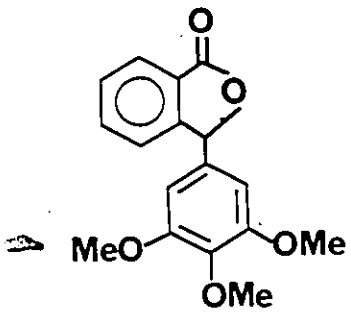
Tetrahydrofuran (THF) was always distilled over benzophenone/sodium under nitrogen immediately prior to use. All other solvents were of reagent grade quality or distilled.

Thin layer chromatography (TLC) was performed on Merck 60F 254 precoated silica plates of 0.25 mm thickness. Column chromatography was performed using Baker 60-200 mesh silica gel as the adsorbent. Microanalyses were carried out by Guelph Chemical Laboratories Ltd. in Guelph, Ontario.

Normal workup involved pouring the reaction mixture into water

or saturated ammonium chloride, extracting three times with ether or methylene chloride, drying the organic extracts with magnesium sulfate and evaporating the solvents on a rotary evaporator.

Preparation of the 3-(3,4,5-trimethoxyphenyl)phthalide 51



n-Butyllithium (10.9 ml,26.3 mmol), as a solution in hexane, was added dropwise to a stirred solution of o-bromobenzoic acid (2.52 g, 12.5 mmol) in 50 ml of dry THF at -100° (ether/CO_2 bath) under N_2. After stirring for 5 minutes at -100°, 3,4,5-trimethoxy benzaldehyde (2.46 g, 12.5 mmol) dissolved in 20 ml of THF was added dropwise. The mixture was stirred for an additional 15 minutes at -100° and then the cold bath was removed. After a further 15 minutes, 6N HCl (75 ml) was added and the entire mixture was warmed to room temperature. Ether was added and the layers were separated. The aqueous layer was extracted with ether (2 X 20 ml). The combined organic phases were washed with H_2O (2 X 25 ml), saturated NaCl (30 ml), and dried over $MgSO_4$. Removal of the solvent and recrystallization from ether/hexane afforded the lactone 51 (2.41 g, 64.3%) as a white powder.

51 $C_{17}H_{16}O_5$: 300.31

mp. 125-127°

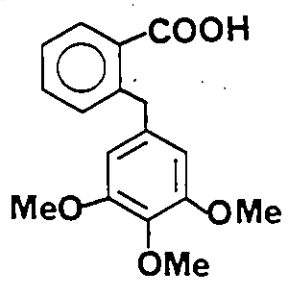
^{1}H NMR: δ(ppm) 3.84 (s,6H), 3.86 (s,3H), 6.35 (s,1H)
6.48 (s,2H), 7.23 - 8.27 (m,4H)

M.S.: m/e 300 (M^+)

IR ($CHCl_3$) λ_{max} (cm^{-1}) 1785 (s)

Analysis: Calculated: C: 67.99 H: 5.37 Found: C: 68.06 H: 5.42

Preparation of o-(3,4,5-trimethoxybenzyl)benzoic acid 52



The lactone 51 (2.41 g, 8.03 mmol) was dissolved in 50 ml toluene. Excess cyclohexene (15 ml) and 10% Pd/C (500 mg) were added and the solution was refluxed for 22 hours. During the reflux time an additional 10 ml of cyclohexene was added. After cooling, filtering, and rotary evaporation of the solvent, the acid 52 (2.40 g, 98.9%) was isolated as white needles.

52 $C_{17}H_{18}O_5$ 302.33

mp. 141.6-143.5°

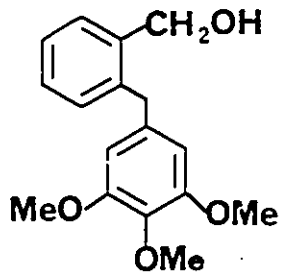
^{1}H NMR: δ (ppm) 3.83 (s,6H), 3.85 (s,3H), 4.39 (s,2H)
6.41 (s,2H), 7.19 - 8.07 (m,4H)

M.S.: m/e 302 (M^+)

IR:($CHCl_3$) λ_{max} (cm^{-1}) 2500-3290 (br), 1705 (s)

Analysis	Calculated:		Found:	
	C: 67.54		C: 67.60	
	H: 6.00		H: 6.09	

Preparation of o-(3,4,5-trimethoxybenzyl)benzyl alcohol 53

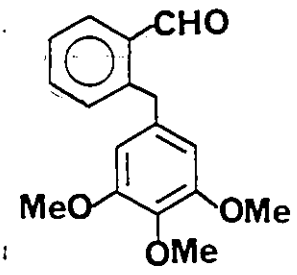


The acid 52 (2.00 g, 6.6 mmol) was dissolved in 25 ml THF and added slowly to a stirred solution of LAH (0.25 g, 6.6 mmol) in 25 ml of THF at 0°. The reaction mixture was stirred for 30 minutes at room temperature and subsequently refluxed for 2 hours. Workup in the usual manner afforded a yellow oil. The oil was

dissolved in ether and the alcohol 53 was precipitated as a yellow solid by the addition of hexane. The yield was 91% (1.73g).

53	$C_{17}H_{20}O_5$	288.34
mp.	138-141°	
^{1}H NMR:	δ (ppm)	3.83 (s,6H), 3.85 (s,3H), 4.35 (s,2H) 4.63 (s,2H), 6.40 (s,2H), 7.22 - 8.01 (m,4H)
M.S.:	m/e 288 (M^+)	
IR:($CHCl_3$)	λ max (cm^{-1})	3450 - 3650 (br)

Preparation of o-(3,4,5-trimethoxybenzyl)benzaldehyde 54



i) The alcohol 53 (1.66 g, 5.76 mmol) was dissolved in 25 ml CH_2Cl_2 and added dropwise to a suspension of pyridinium chloro-

chromate in 10 ml CH_2Cl_2 at 0°. The reaction mixture was warmed to room temperature and stirred overnight. Evaporation of the solvent resulted in a solid which was purified via column chromatography (1:2 ethyl acetate/hexane). Recrystallization from ether/hexane afforded the aldehyde 54 (1.53 g, 93.2%) as white prisms.

ii) Freshly prepared MnO_2 (1.00 g) was added to a solution of the alcohol 53 (1.52 g, 5.28 mmol) in 25 ml CH_2Cl_2 and subsequently stirred at room temperature for 8 hours. The reaction was filtered and fresh catalyst (500 mg) was added. Stirring for an additional 8 hours was followed by filtration and removal of solvent in vacuo. The solid thus obtained was recrystallized from ether/hexane to give the aldehyde 54 (1.42 g, 94%).

54 $C_{17}H_{18}O_5$ 286.33

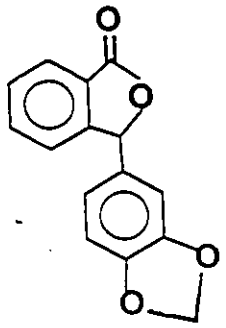
mp. 143.4-146.0°

^{1}H NMR: δ (ppm) 3.83 (s,6H), 3.86 (s,3H), 4.37 (s,1H) 6.40 (s,2H), 7.23 - 8.00 (m,4H), 9.70 (s, 1H)

M.S.: m/e 286 (M^+)

IR:($CHCl_3$) λ_{max} (cm^{-1}) 1698 (s)

Preparation of the 3-(3,4-methylenedioxyphenyl)phthalide 55



The lactone 55 was prepared as described above for the preparation of 51. The reagents and their amounts used were: n-butyllithium (19.5 ml, 51.2 mmol), o-bromobenzoic acid (4.91g, 24.4 mmol) in 100 ml of dry THF, piperonal (3.70 g, 24.4 mmol) in 40 ml of dry THF, and 150 ml 6N HCl. Normal workup and recrystallization from ether/hexane afforded the lactone 55 (3.84g, 62%) as a white solid.

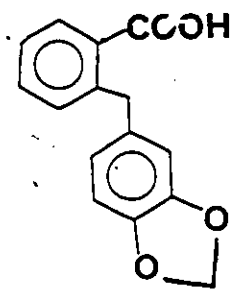
55 $C_{15}H_{10}O_4$ 254.24

mp. 161.2 - 163.1

1H NMR: δ(ppm) 5.92 (s, 2H), 6.34 (s, 1H), 6.45-6.68 (m, 3H), 7.10-7.25 (m, 2H), 7.39-7.42 (m, 1H), 7.98-8.01 (d,1H).

IR:($CHCl_3$ λ_{max} (cm^{-1}) 1735

Preparation of o-(3,4-methylenedioxybenzyl)benzoic acid 57



The acid 57 was prepared in the same manner as the acid 52. The reagents and amounts used were: lactone 55 (1.05g, 4.2 mmol) in 50 ml of toluene, cyclohexene (12.5 ml), and 10% Pd/C (250 mg). Filtration and solvent removal furnished the acid 57 (1.06g, ~99%) as white prisms.

57 $C_{15}H_{12}O_4$ 256.23

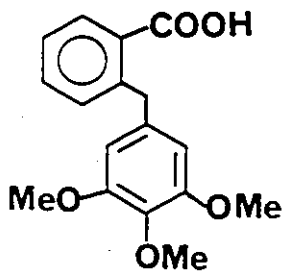
mp. 116.2-118.3°

^{1}H NMR: δ (ppm) 4.36 (s,2H), 5.98 (s,2H), 6.48 - 6.70 (m,3H), 7.16 - 7.30 (m,2H), 7.40 - 7.46 (m, 1H), 7.98 - 8.02 (d, 1H).

M.S.: m/e 256 (M^+)

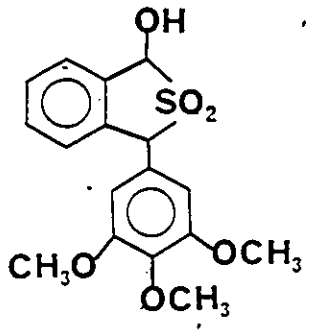
IR:($CHCl_3$) λ_{max} (cm^{-1}) 3650 (s)

Direct conversion of o-bromobenzoic acid to the acid 52



The procedure used for the preparation of the lactone 51 was followed using o-bromobenzoic acid (1.08g, 5.4 mmol), n-BuLi (4.7 ml, 11.3 mmol), and 3,4,5-trimethoxybenzaldehyde (1.05g, 5.4 mmol). Workup and evaporation were immediately followed by the hydrogenolysis reaction. Thus the crude oil obtained was dissolved in 40 ml of toluene and cyclohexene (10 ml) and 10% Pd C (220mg) were added. The mixture was refluxed overnight, filtered, and the solvent was removed in vacuo. The oil remaining was taken up in ether (40ml) and washed with 5% $NaHCO_3$ (2 X 15 ml). The aqueous layer was acidified to yield a white precipitate, which when dried, was characterized as the acid 52. The yield was 60% (0.965g) starting from o-bromobenzoic acid. All spectral data were identical to that presented earlier.

Preparation of (±)1-hydroxy-3-(3,4,5-trimethoxyphenyl)-1,3-dihydrobenzo[c]thiophene-2,2-dioxide



The aldehyde 54 (0.34g, 1.22 mmol) was dissolved in 50 ml of benzene and placed in a quartz tube. The solution was flushed with nitrogen and then saturated with SO_2. The mixture was irradiated for 3 hours after which the solvent was removed. The remaining oil was washed with hexane to give the hydroxy sulfone 59 (0.234g, 55%) as a brownish solid.

The hexane layer was evaporated in vacuo to leave a white solid that was characterized as the anthracene derivative 59'.

59 $C_{17}H_{18}O_6S$ 350.39

mp. 45.4-46.3° (dec.)

^{1}H NMR:

Isomer 1:

δ (ppm) 3.78 (s,3H), 3.80 (s,6H), 5.32 (s,1H)
5.72 (s,1H), 7.20 - 7.98 (m,4H)

Isomer 2:

δ (ppm) 3.79 (s,3H), 3.83 (s,6H), 5.47 (s,1H)
5.68 (s,1H), 7.19 - 7.98 (m,4H)

M.S.: m/e 286 (M^+)

IR:($CHCl_3$) λ_{max} (cm^{-1}) 3500 (s) and 1530

59 $C_{17}H_{16}O_5$ 268.32

^1H NMR: δ (ppm) 4.02 (s,3H), 4.06 (s,3H), 4.52 (s,3H),
7.44 - 7.47 (br,2H), 7.88 - 8.21
(m, 3H), 8.64 (s,1H), 8.68 (s,1H)

M.S.: m/e 268 (M^+)

Attempted coupling of 59 with the isocyanate of methyl 4-amino-crotonate

i) The hydroxy sulfone 59 (50mg, 0.14 mmol) was dissolved in CH_2Cl_2 (10ml). The isocyanate (20.1 mg, 0.143mmol) and triphenyl-tin acetate (5.8mg, 0.014mmol, 10 mol%) were added. The reaction mixture was stored at room temperature for several hours and subsequently the mixture was concentrated down to an oil. Methylene chloride (10 ml) was added and again the reaction

vessel was stored at room temperature for several hours. This procedure of concentration and dilution was repeated several times. The progress of the reaction was followed by IR until the band at 2240-2270 cm^{-1} had totally disappeared. The CH_2Cl_2 was removed and the resulting oil was purified via column chromatography using ethyl acetate as the solvent. A small amount (6.1 mg, 10%) of material suspected to be the urethane 63 on the basis of the NMR was isolated.

^{1}H NMR: δ (ppm) 3.72 (s,3H), 3.76 (s,3H), 3.81 (s,6H) 4.02 (m,2H), 4.36 (t,1H), 4.91 (m,1H) 5.43 (d, 1H), 5.95 (d,1H), 7.20 - 7.99 (m,4H)

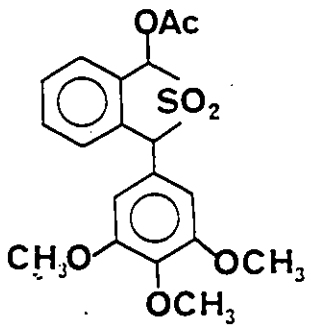
ii) The above procedure was repeated on the sulfone 59 (65 mg), the isocyanate (1 eq., 26.24 mg), and triphenyltin acetate (1.2 eq., 91.1 mg) in CH_2Cl_2. After purification, none of the desired urethane was isolated.

iii) The procedure was again repeated using the sulfone 59 (15 mg), the isocyanate (1 eq., 6.04 mg), and 10 mole percent of triphenyltin acetate (1.7 mg) in acetonitrile.

After purification, no urethane was isolated.

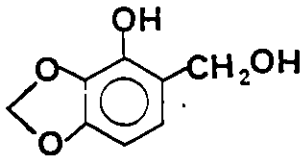
iv) The procedure was again repeated using 51.4 mg of sulfone, 20.6 mg of isocyanate, and 6 mg of the catalyst in CH_2Cl_2. The reaction temperature was adjusted to 30°. No urethane was isolated after column chromatography of the crude reaction mixture.

Attempted preparation of 1-acetyl-3-(3,4,5-trimethoxyphenyl)-1,3-dihydrobenzo[c]thiophene-2,2-dioxide



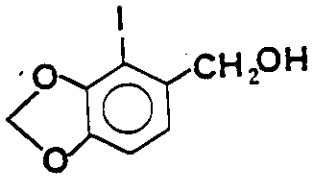
The sulfone (75 mg) was dissolved in 25 ml of acetic anhydride and allowed to stand at room temperature for 5 hours. TLC and ^1H NMR indicated that extensive decomposition had occurred.

Attempted preparation of 2-hydroxy-piperonol 67



Piperonol (500 mg, 3.3 mmol) was dissolved in 15 ml of dry THF and cooled to 0° under nitrogen. A solution of n-BuLi in hexane (2.89 ml, 2.2 eq., 2.4 M) was added dropwise. After two hours oxygen was bubbled directly into the reaction mixture. Normal workup was followed by extraction with a 10% KOH solution (2 x 10 ml). The organic solvent was dried and removed in vacuo. None of the desired phenol was obtained after chromatographic separation.

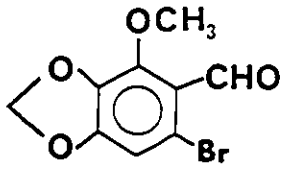
Attempted preparation of 2-iodo-piperonol 69



Piperonal (530 mg, 3.5 mmol) was dissolved in 15 ml of dry THF and cooled to 0°. The dianion was generated under nitrogen as

described for the attempted preparation of 67 (nBuLi (3.06 ml), 2h, 0°) and was reacted with iodine (1 eq., 440 mg) dissolved in THF. Normal workup followed by treatment with Na_2SO_4 did not yield the expected iodide.

Preparation of 6-bromo-2-methoxy-piperonal 71



2-Methoxy-piperonal (1.15g, 6.4 mmol) was treated with 1.2 g of bromine in glacial acetic acid. The reaction mixture was stirred at room temperature for 24 hours. Precipitation with water and filtration afforded a crude solid that was recrystallized from CH_2Cl_2/hexane to yield 1.24g (75%) of 71 as colorless crystals.

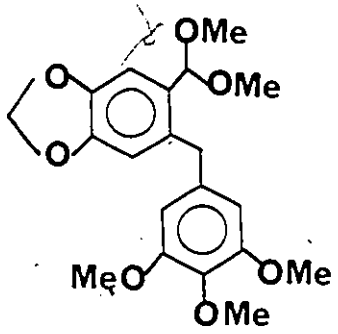
71 $C_9H_7O_4Br$ 259.03

mp. 138.2-139.8°

^{1}H NMR: δ (ppm) 3.97 (s,3H), 5.95 (s,2H), 6.82 (s,1H) 10.48 (s,1H)

IR:($CHCl_3$) λ_{max} (cm^{-1}) 1690 (s)

Preparation of 6-(3,4,5-trimethoxybenzyl)piperonal dimethyl acetal via the Glinski coupling reaction

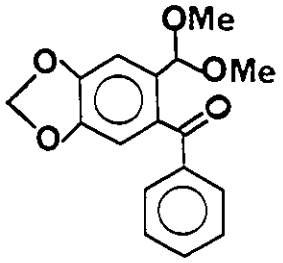


6-Bromopiperonal dimethyl acetal (450 mg, 1.6 mmol) was dissolved in 10 ml of dry THF and cooled to -78° under N_2. n-BuLi (0.54 ml, 1.1 eq., 2.6 M in hexane) was added and the solution was stirred for 10 minutes. TMEDA (1 eq., 0.24 ml) and then n-Bu_3PCuI (310 mg, 0.8 mmol) were added sequentially in a small volume of THF. 1-Bromomethyl-3,4,5-trimethoxybenzene (0.21g, 0.9 mmol) in THF was next added and the reaction mixture was stirred for 5 min. at -78° and then warmed to RT. After 1 hour, the reaction was worked up in the usual manner. Column chromatography (3:1 hexane/ethyl acetate) afforded 74 (186 mg, 31%) as a colorless oil.

74 $C_{20}H_{22}O_7$ 374.38

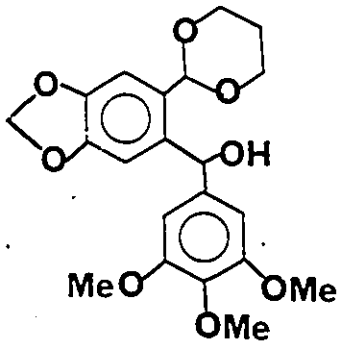
^1H NMR: δ (ppm) 3.27 (s,3H), 3.80 (s,9H), 3.92 (s,2H), 5.89 (s,2H), 5.92 (s,1H), 6.35 (s,2H), 6.44 (s, 1H), 7.10 (s,1H)

Attempted preparation of 6-benzoyl-3,4-methylenedioxy benzaldehyde dimethyl acetal 75



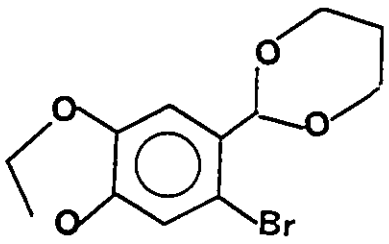
6-Bromopiperonal dimethyl acetal (350 mg, 1.3 mmol) was dissolved in 15 ml of dry THF. Under nitrogen, the solution was cooled to -78°. n-BuLi (0.54 ml, 1.1 eq., 2.6 M solution in hexane) was added dropwise and the mixture was stirred for 15 minutes at -78°. Freshly distilled benzoyl chloride was added and the solution was allowed to warm to room temperature. Normal workup followed by column chromatography (ether/hexane/ethyl acetate) gave none of the desired ketone 75.

Attempted preparation of 6-(α - hydroxy 3,4,5-trimethoxybenzyl) 3,4-methylenedioxy benzaldehyde dimethyl acetal 76



The anion was prepared as described for the attempted preparation of 75 using the following reagents: 6-bromo-piperonal dimethyl acetal (365 mg, 1.3 mmol), n-BuLi (1.1 eq., 0.56 ml). The anion was reacted at -78° with 3,4,5-trimethoxy-benzaldehyde (1 eq., 250 mg) dissolved in dry THF. The reaction was then warmed to room temperature. Normal workup was followed by attempted purification. ^1H NMR indicated that none of the desired alcohol had formed.

Preparation of 6-bromo-3,4-methylenedioxy benzaldehyde trimethylene ketal 77



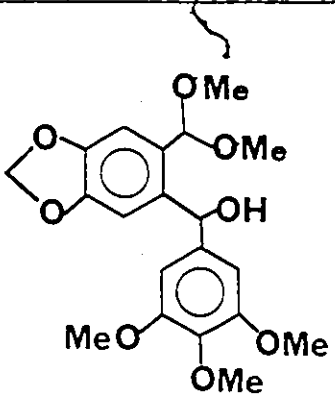
Bromopiperonal (10.0g, 0.04 mol) was dissolved in excess trimethylene glycol (200 ml). A catalytic amount of p-TsOH (approx. 12 mg) was added. The mixture was refluxed for 18 hours and normal workup afforded the ketal 77 (10.11g, 88%) as white crystals.

77 $C_{11}H_{11}O_4Br$ 287.13

^{1}H NMR: δ (ppm) 1.40 -1.60 (dt,2H), 4.00 -4.28 (m,4H) 6.00 (s,1H), 6.15 (s,2H), 7.09 (s,1H), 7.19 (s, 1H)

M.S.: m/e 287 (M^+)

Preparation of 6-(α -hydroxy 3,4,5-trimethoxybenzyl)-3,4 methylenedioxy benzaldehyde trimethylene ketal 78



The ketal 77 (0.55g, 2 mmol) was dissolved in 35 ml of THF and cooled to -78° under nitrogen. A solution of n-BuLi in hexane (1.2 eq) was added dropwise. The anion thus produced was reacted at -78° with 3,4,5-trimethoxybenzaldehyde (0.59g, 2 mmol) dissolved in THF. The reaction mixture was warmed to room temperature. Normal workup followed by column chromatography yielded the alcohol 78 (0.53g, 68%) as a white solid.

78 $C_{21}H_{24}O_7$ 388.42

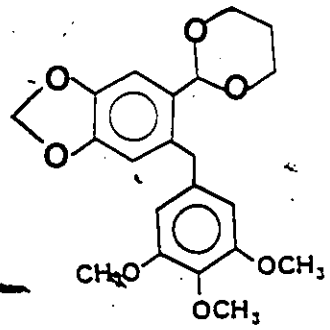
mp. 135.4-137.0°

^{1}H NMR: δ (ppm) 1.42 -1.61 (dt,2H), 4.04 - 4.24 (m,4H)
3.81 (s,3H), 3.82 (s,6H), 6.01 (s,1H)
6.14 (s,2H), 6.38 (s,2H), 6.50 (s,2H)
7.10 (s,1H), 7.21 (s,1H)

M.S.: m/e 388 (M^+)

IR:($CHCl_3$): λ_{max} (cm^{-1}) 3650 (s)

Attempted preparation of 3,4-methylenedioxy-6-(3,4,5-trimethoxybenzyl) benzaldehyde trimethylene ketal 79



i) Hydrogenolysis

The alcohol 78 was dissolved in toluene (10 ml) and excess cyclohexene (10 ml) was added. To this solution 25 mg of 10% Pd/C was added. The suspension was then refluxed overnight (16 hours) after which it was filtered to remove the catalyst. The solvent was evaporated and the ^{1}H NMR of the crude product indicated that 79 had not formed.

ii) The alcohol 78 (200 mg, 0.52 mmol) was dissolved in 5 ml of pyridine and cooled to 0°. $SOCl_2$ (0.114 ml) was added dropwise. The mixture was warmed to RT and stirred for 15 minutes. The pyridine was removed and the crude product was redissolved in dry THF. This solution was then added to a suspension of LAH (24 mg, 0.62 mmol) in THF at 0°. After the bubbling had stopped, the reaction was warmed to RT. The reaction was worked up in the usual manner. The ^1H NMR of the crude product indicated that decomposition had occurred and that 79 had not been formed.

iii) The alcohol 78 (100mg, 0.2 mmol) was dissolved in 2 ml of CH_2Cl_2 and cooled to -20°. Mesyl chloride (CH_3SO_2Cl) (0.031 ml, 0.37 mmol, 1.5 eq) was added to the alcohol. Immediately after, triethylamine (0.069 ml, 0.495 mmol, 2 eq) was added to the reaction. After 5 minutes, the methylene chloride was evaporated without heating. The crude product was redissolved in dry THF and quickly added to a solution of LAH (11 mg, 0.3 mmol) in THF at 0°. After the bubbling stopped, the reaction was warmed to RT and worked up in the usual manner. According to the ^1H Nmr, the desired 79 had not formed.

iv) Barton-McCombie reaction

The alcohol 78 (223 mg, 0.57 mmol) was dissolved in THF and added to a suspension of NaH (20 mg, 1 eq.) and imidazole (38 mg) in THF at 0°. After the addition was complete, the solution was refluxed for 20 min. after which carbon disulfide (1 ml) and methyl iodide were added in succesion. This solution was then refluxed for two hours. The reaction mixture was cooled and washed with water. The solvent was removed to yield a brownish oil. The oil was redissolved in toluene and added to an already refluxing solution of tributyltin hydride (166 mg) in toluene. After 6 hours, the toluene was removed. The ^1H NMR indicated none of the desired product had formed.

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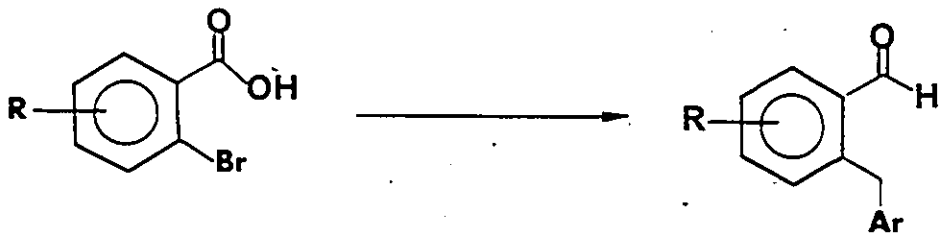
CLAIMS TO ORIGINAL RESEARCH

i) An efficient method for the preparation of aldehydes of the type (i) starting with ortho-haloaromatic acids was developed.



ii) The photolysis of (i) R=H, Ar=3,4,5-trimethoxyphenyl was carried out in the presence of SO_2. An unstable -hydroxy-sulfone, the result of the trapping of an ortho-quino-dimethane with SO_2, was isolated.

iii) 6-Bromo-2-methoxy-3,4-methylenedioxy benzaldehyde, a potential intermediate in the synthesis of -peltatin, was prepared.

iv) Halogen metal exchange in 6-bromopiperonal trimethylene ketal was studied. The 6-lithio derivative prepared from the trimethylene ketal was found to be more stable than that of the dimethyl ketal.