Applications Of The Salicylidene-thiolactone Rearrangement: Pseudo-cannabinoid Development.

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APPLICATIONS OF THE SALICYLIDENE-THIOLACTONE REARRANGEMENT: PSEUDO-CANNABINOID DEVELOPMENT

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APPLICATIONS OF THE SALICYLIDENE-THIOLACTONE REARRANGEMENT: PSEUDO-CANNABINOID DEVELOPMENT

by

Peter R. Seoane

A Dissertation
Presented to the Graduate Committee
of Lehigh University
in Candidacy for the Degree of
Doctor of Philosophy
in
Chemistry

Lehigh University
1984

CERTIFICATION OF PRESENTATION

This dissertation is respectfully submitted to the Graduate Faculty of Lehigh University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Peter R Seoane

Peter R. Seoane

A CERTIFICATE OF APPROVAL

Approved and recommended for acceptance as a dissertation in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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ACKNOWLEDGEMENTS

The author expresses his sincere gratitude to the chemistry faculty at Lehigh University for their contributions to his graduate education. Especially appreciated are the efforts of Dr. Ned D. Heindel and Dr. G. Doyle Daves, Jr. Appreciation is expressed to Mr. William Anderson for aid in obtaining NMR spectra and Mass spectra, Dr. Charles S. Kraihanzel for performing MMI caluclations, and Mrs. Mary Ann Elgin for typing this manuscript.

The author wishes to dedicate this thesis to his wife, Frances, whose sacrifices have made this work possible and his daughter, Kira, who makes it all worthwhile.

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ABSTRACT

The unique and diverse biological activities of tetrahydrocannabinol (Δ^9-THC) have generated considerable interest in analog development, both to enhance and separate these activities. Work in the area of analgetic THC analog development has led to the advancement of a 3 point receptor fit theory, which has successfully been applied to the development of new analgetic cannabinoids. Application of this theory in the heterocyclic series suggests that pseudocannabinoids based on the thieno[3,2-c][1]benzopyran ring system would demonstrate significant analgetic activity.

A synthetic route to this ring system, based on the salicylidene-thiolactone rearrangement was developed and tested in model systems, demonstrating the suitability of this approach to the synthesis of this new class of pseudocannabinoids. Product distribution and stereochemistry were determined by NMR spectroscopy and mass spectroscopy, and a mechanism rationalizing the results was devised.

Modification of the reaction scheme used in the model compounds to allow the incorporation of a 9-hydroxy group led to the preparation of a novel cannabinoid bearing a sulfoxide moiety, 9-hydroxy-4,4-dimethyl-7-(1,1-dimethylheptyl)-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran-S-oxide. The relative sterochemistry of this compound was determined by ASIS NMR spectroscopy and the minimum energy conformation was determined using

Allinger's model. These data were used to compare the structure of this pseudocannabinoid to the structural requirements for the presumed cannabinoid receptor.

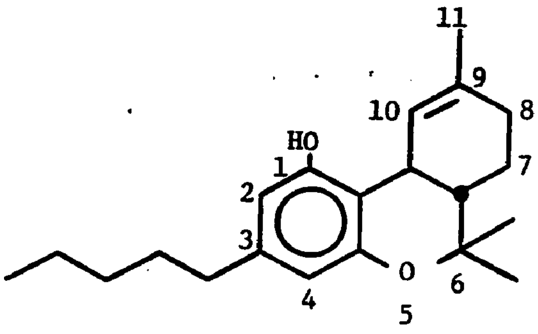
"My reason for emphasizing natural products is that they remain one of the few <u>de novo</u> sources of drug discovery. Their direct medicinal value is rare and should really not be expected because natural products, with the exception of the mammalian hormones, arise from the metabolism of organisms far removed from the evolutionary stages of man and metabolically related animals. As far as can be estimated, they have not been intended to be used as therapeutic agents. However, their unorthodox and often unexpected chemical structures derived from universal metabolites offer novel points of departure for molecular modification which, in many cases, has led to clinically valuable drugs."

Alfred Burger [1]

INTRODUCTION

Extracts from *Cannabis sativa* (marijuana) have been used for over 5000 years for a variety of medicinal and social reasons [2]. Folkloric precedent may be found for the therapeutic value of marijuana in the treatment of at least 14 ailments [3], including insomnia, neuralgia, migraine pain, rheumatism, asthma, bronchitis, anorexia, and gynecological disorders [4]. Smore recent anecdotal evidence for the medicinal value of marijuana comes from illicit users of this drug, who suggest its ability to provide relief from the symptoms of glaucoma and nausea. The validity of these observations was confirmed by Hepler and Frank [5], who were able to show that smoking of marijuana resulted in lowered intraoccular pressure, and Sallan [6], who demonstrated the efficacy of oral THC therapy in the relief of nausea.

Despite these folkloric leads, and some early efforts toward synthetic analog development [7], the pharmacological profile of cannabis components as well as a variety of other potentially biologically active compounds. This cloud only began to clear in the late 60's when the active principle of marijuana, tetrahydrocannabinol (Δ^9-THC), became available in pure form [8,9].



Δ^9 - THC

The diverse biological activities evidenced by Δ^9-THC led to the synthesis [10] and evaluation [11] of a wide range of natural cannabinoids and their structural analogs in an effort to gain enhanced activity and specificity of action. From these studies a general structure-activity relationship (SAR) was developed [4,7]. These parameters, given below, are the result of structural modifications of the tetrahydrocannabinol nucleus as shown in Figure 1, and are based on generalized CNS effects as evidenced by a post-dosage phenomenon of relaxed staring accompanied by hypersensitivity to external stimuli [12]. Since these properties are peculiar to cannabinoids regardless of other activities that they may ellicit, these data are valid only in the broadest sense.

STRUCTURAL MODIFICATION OF THE THC NUCLEUS

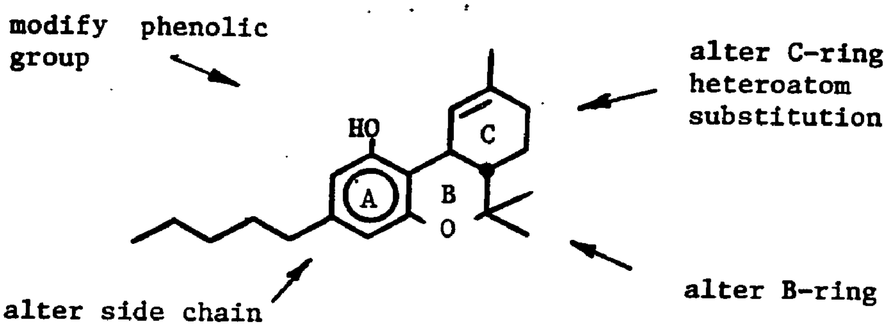


Figure 1

SAR CONCLUSIONS

1. Basic structure:

A benzopyran nucleus with an aromatic C1 hydroxyl group and a C3 alkyl or alkoxy group is required for activity.

2. Phenolic group modificiation:

The phenolic group may be esterified without loss of activity. Etherification results in inactive compounds. Heteroatom replacement reduces (NH_2) or eliminates (SH) activity.

3. Side chain modification:

A minimum side chain length of n-pentyl is required for activity. Increased chain length (heptyl) and side chain branching near the aromatic A ring increase activity. Alkoxy and p-fluorophenylalkyl side chains are active.

4. B-ring modificiation:

The pyran ring may be expanded by one carbon without loss of activity but may not be opened. The pyran O may be replaced by N with retained but reduced activity. The gem-dimethyl groups at C6 are optimal for activity. One of these methyl groups may be replaced by hydroxymethyl.

5. C-ring modification:

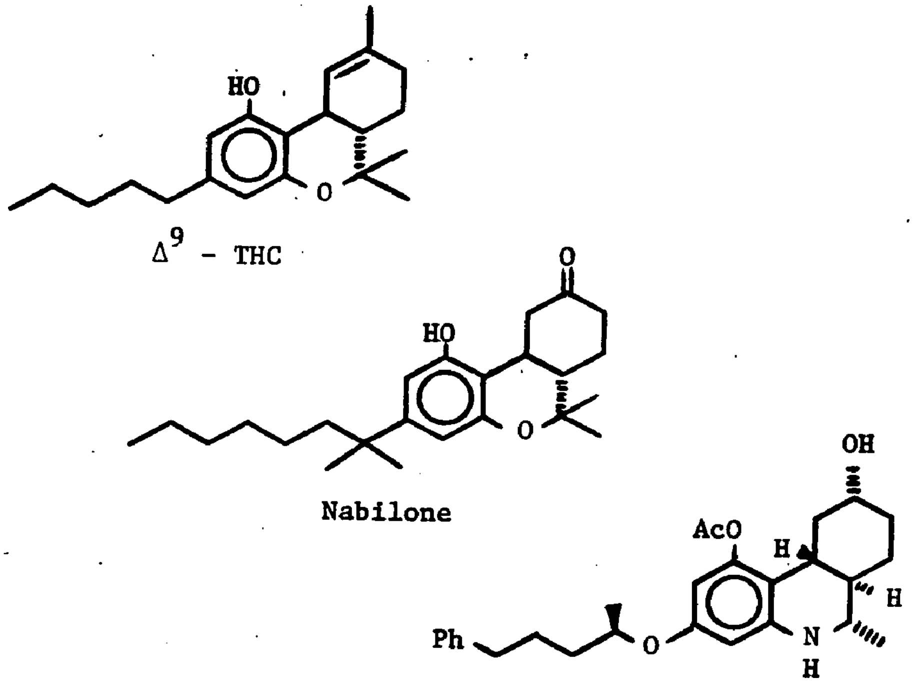
> Heteroatom substitution is acceptable (N,S). The most active compounds have the heteroatom in a phenethylamine orientation. Unsaturation (Δ^8, Δ^9, Δ^{6a}) retains activity. *Trans* ring-fused compounds are more active than *cis*-fused compounds. C-9 methyl groups result in increased activity.

Continued study of these THC-derived agents has led to the identification of several key areas of therapeutic potential [13]. Two of these, antiemetic activity and analgesia, appear particularly promising and are discussed below.

Antiemetic activity

The antiemetic properties of natural Δ^9-THC, having been clinically confirmed [6], have prompted the National Cancer Institute to make this otherwise illegal substance available for the relief of cancer chemotherapy-induced nausea under certain circumstances [14]. Unfortunately, Δ^9-THC is no better than other clinically available antiemetics in the treatment of the symptoms induced by the strongly emetogenic anti-cancer agents *cis*-platin [15], the nitrogen mustards [16], and nitrosoureas [16].

Antiemetic Cannabinoids



Δ^9 - THC

Nabilone

Levonantradol

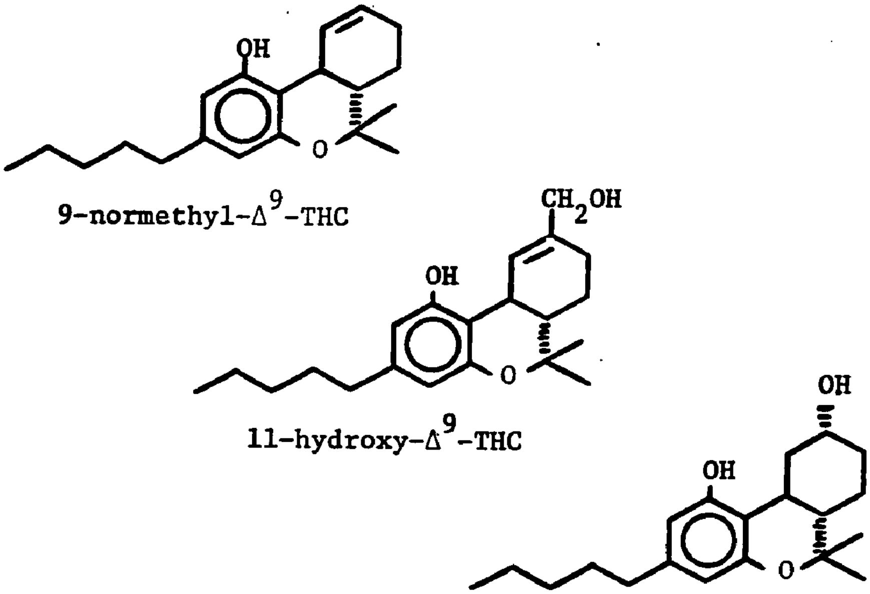
Figure 2

Nabilone, commercially available as an antiemetic agent in Canada and Sweden, has the advantages of not being internationally controlled, and showing activity against cisplatin induced nausea [17]. It has also been shown to be superior to the other synthetic of interest, levonantradol [18]. While a great deal of structural variance may be seen in these compounds, three key areas of similarity may be noted, i.e., the presence of a lipophilic side chain, a phenolic OH, and an aliphatic hydroxyl group proximal to the phenolic moiety (or a methyl group, similarly located, that may be metabolically hydroxylated). The significance of these similarities will be addressed presently.

Analgesic activity

The 50-year search for the ideal analgetic [2] has taken the medicinal chemist to the cannabinoids. While the weakly analgetic Δ^9-THC does not show real therapeutic value, in part due to unacceptable side effects [19], there appears to be some promise for the development of a THC derived analgesic agent [4,20]. The work of Wilson and May [21,22,23] led to the hypothesis that the analgetic activity of Δ^9-THC is due to the metabolic hydroxylation of the 11-methyl group. This supposition gains credence in light of the fact that 9-nor methyl Δ^9-THC is poorly analgetic, but 9-normethyl-9β hydroxyhexahydrocannabinol (HHC) is as analgetic as morphine.

Cannabinoids + Analgesia



9-normethyl-Δ^9-THC

11-hydroxy-Δ^9-THC

9-β-hydroxy-HHC

Figure 3

Replacement of the 11-methyl group by a carboxylic acid group results in an inactive compound, suggesting that the role of the aliphatic hydroxyl group at a potential receptor is a non-acidic one.

Following the lead of Wilson and May, Johnson and Milne [19] embarked on a study to further delineate the analgetic SAR in cannabinoids using HHC as the model system. Their results follow:

Analgetic SAR

1. Side chain modification:

Three side chains are essentially equiactive, i.e.

1,1-dimethylheptyl
1,2-dimethylheptyl
$O-CH(CH_3)-(CH_2)_3-Ph$

2. Phenolic group modification:

Esterification is acceptable, but other alterations or substitutions result in a substantial loss of activity.

3. B-ring modifications:

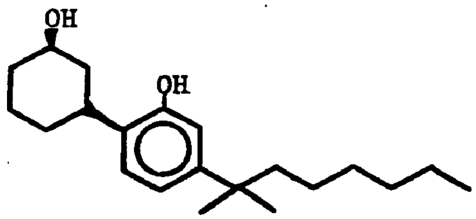
The pyran O may be replaced by NH, and one of the geminal methyl groups may be removed without significant loss of activity.

4. C-ring modifications:

The C9-hydroxyl groups is required, compounds with an equitorial OH are more active than their axial isomers.

The above observations were used in the design of levonantradol (see Fig. 2 for structure) [24,25], an analgetic cannabinoid that is approximately 7 times as potent as morphine [19].

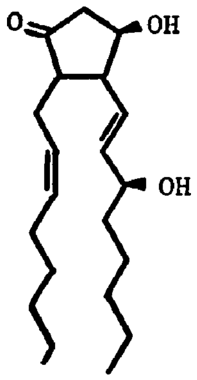
Encouraged by this success, Milne and Johnson advanced a 3-point receptor fit theory for analgetic activity in the cannabinoids [26], and tested it with the synthesis of a compound incorporating only the suggested minimal functional group requirements of a lipophilic side chain, a phenolic moiety, and a proximal aliphatic hydroxyl group. This compound, shown below, bears a strong conformational and spatial resemblance to HHC as shown by comparison of



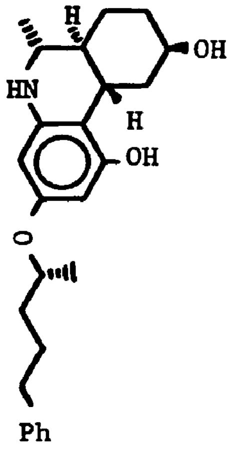
molecular models and minimum energy conformation calculations (Allinger's molecular mechanics calculation program, MMI) [3,27]. Biological testing determined that this novel ring opened cannabinoid analgetic is equiactive with morphine [3].

Cannabinoids - mechanism of action.

Although the mode of action of the cannabinoids remains unknown, the suggestion has been made that some kind of interaction with the prostaglandins may be involved. Depending on the compound involved, and the activity ellicited, cases have been made for both the inhibition and promotion of prostaglandin biosynthesis, as well as for the blockade of prostanoid receptors[28]. Several groups have shown that Δ^9-THC is capable of interfering with prostaglandin biosynthesis [29-32]. In tests aimed at quantifying the degree of such inhibition, the inhibitory effect of the cannabinoids was shown to parallel demonstrated antiinflammatory activity [32]. Eyes treated with arachidonic acid, a key prostaglandin precursor, showed an increase in intraoccular pressure (IOP) that was effectively blocked by pretreatment with Δ^9-THC. Prostaglandin E_2 (PGE_2) induced increases in IOP were not similarly blocked [33]. Milne and Johnson compared space filling models and x-ray crystallographic data for levonantrodol and PGE_2 and noted striking similarities, particularly in the spatial and conformational arrangement of the hydroxyl groups and the relative location of lipophilic alkyl chains (see below) [26].



PGE_2



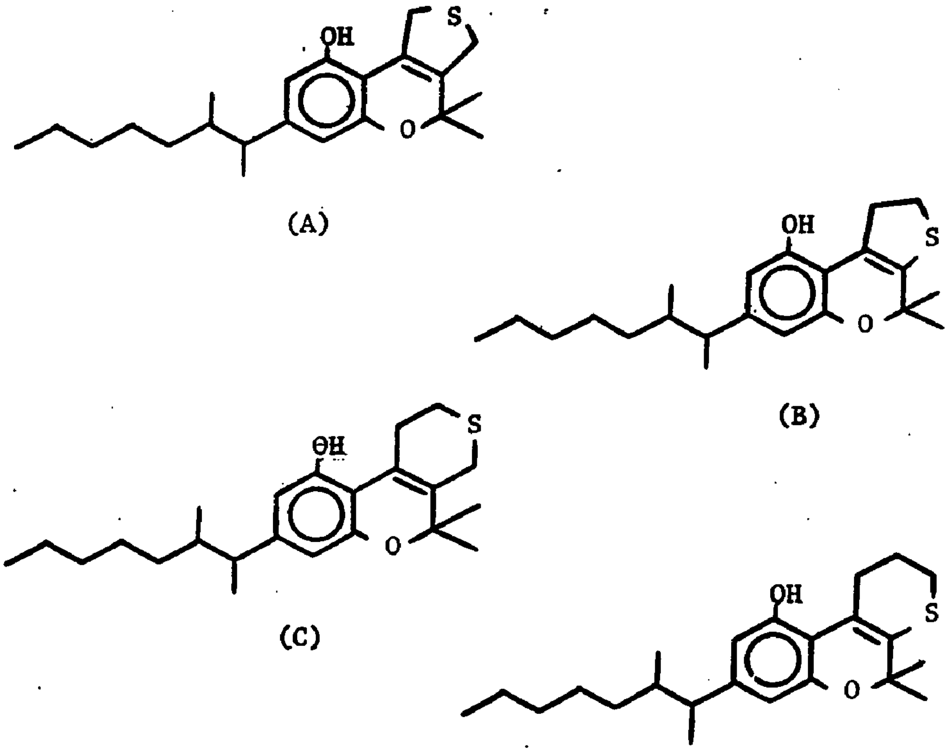
Levonantradol

Occupation of the receptor for PGE_2 could explain the analgetic activity of cannabinoids by initiating the same sequence of events as morphine, which, as suggested by Collier [34], acts through a prostaglandin mediated decrease in cyclic AMP formation. It appears likely, however, that cannabinoids interfere with prostaglandin synthesis at different points as levonantradol is not antagonized by naloxone, a potent blocker of narcotic analgesic agents [26]. The anti-emetic properties of THC's may also be explained through an inhibition of prostaglandin formation, as prostaglandins have been shown to cause emesis in man [35]. The above observations suggest that application of Milne and Johnson's 3-point receptor fit model could prove invaluable in the design of potential non-narcotic analgesic and antiemetic cannabinoids.

Sulfur containing THC analogs:

Razdan and co-workers, in their efforts aimed at the development of heterocyclic cannabinoids, synthesized a series of THC analogs with a sulfur containing C-ring [36,37].

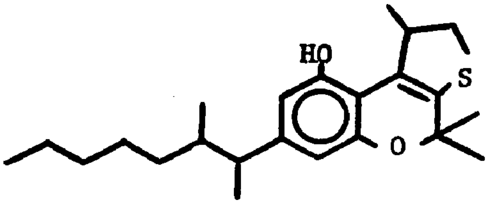
Sulfur-containing THC analogs



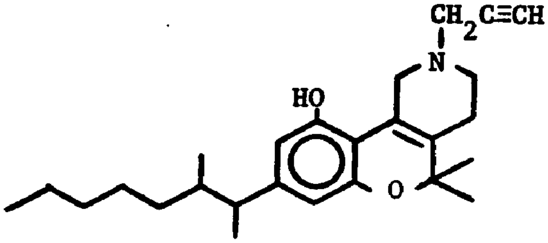
(A) (B) (C) (D)

Figure 4

These dihydrothieno and dihydrothiapyrano THC's are unique in that as a group, they represent some of the most potent non-nitrogen containing analgesic agents known [20]. The best of these, a methyl dihydrothieno THC (E), showed better analgesic activity, under the same testing protocols, than the nitrogen heterocyclic THC (F), which was determined by Razdan to have analgesic activity between that of codiene and morphine [20].

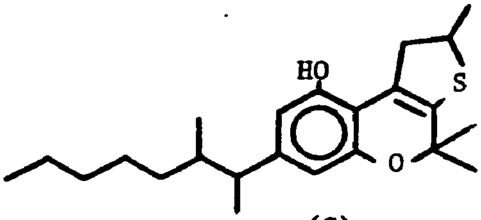


(E)



(F)

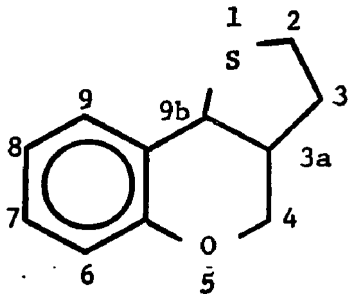
The weak analgetic activity of the des-methyl analog of (E), and the reduced (∿ 10X) activity demonstrated by its regioisomer (G), led Razdan to suggest that a methyl substituent prominal to the phenolic OH group provided optimal activity [38]. This idea was treated in the carbocyclic series with similar results.



(G)

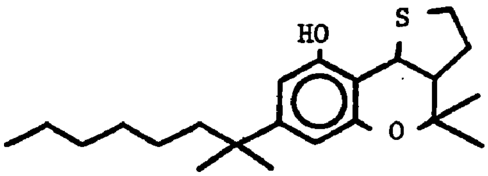
It appears likely that, as in the case of Δ^9-THC, the analgetic activity of (E) derives from the metabolic hydroxylation of the C1 methyl group, providing a compound with greater structural similarity to HHC and one whose structure is in accord with Milne and Johnson's 3-point receptor fit model for analgesic activity in the cannabinoids.

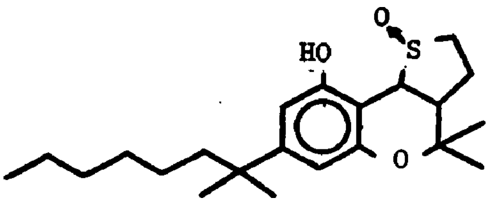
If the receptor role of the phenolic OH in THC's is truly a non-acidic one, the synthesis of thia-THC's with sulfur's electron density in a site more nearly in line with the hydroxyl group of HHC should produce a new series of THC analogs with analgesic and anti-emetic activity. The thieno[3,2-c][1]benzopyran ring system with



sulfur occupying a benzylic site appears to satisfy the above requirements. Even more promising medicinal agents should be available through the oxidation of these compounds to their sulfoxides, providing still better functional group conformational overlap with HHC.

This thesis concerns itself with synthetic studies directed toward the preparation of the tetrahydrothieno[3,2-c][1]benzopyran based THC analogs shown below:

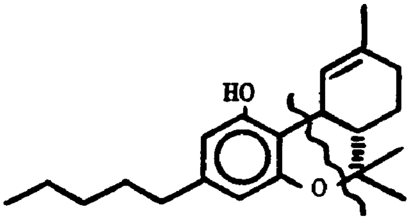




RESULTS AND DISCUSSION

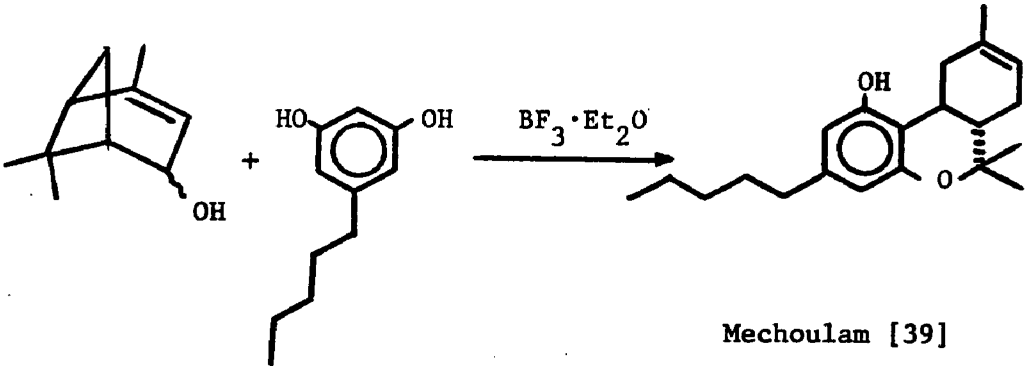
General Synthetic Considerations:

While a great number of synthetic approaches toward the cannabinoids have been developed, the relative simplicity of the THC nucleus has led to two main strategies, based on the key disconnect shown below:

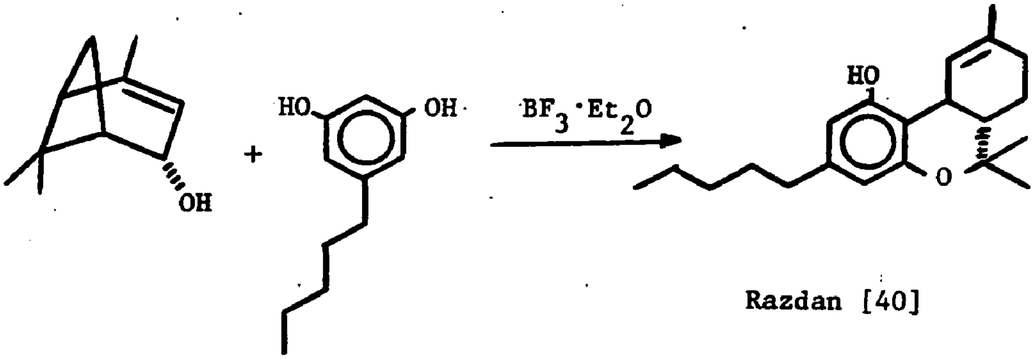


Δ^9-THC

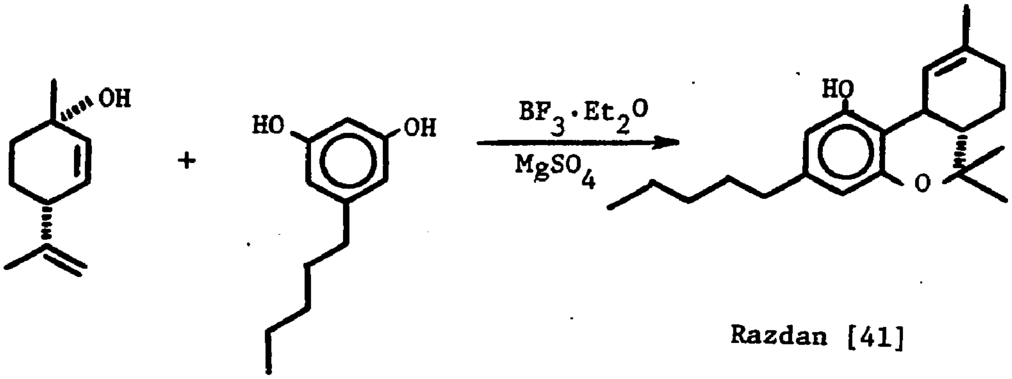
The first approach, and perhaps the most obvious, directly couples an appropriate monoterpene with the alkyl resorcinol olivetol under protic or Lewis acid catalysis. Several examples are given below:



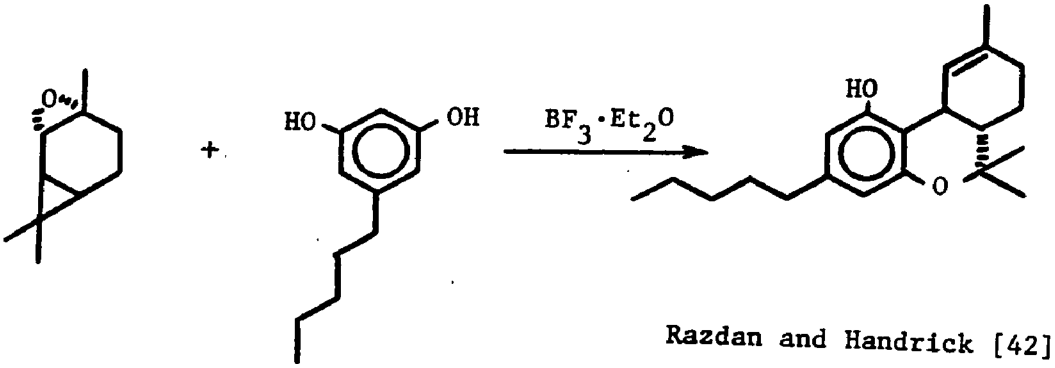
Mechoulam [39]



Razdan [40]



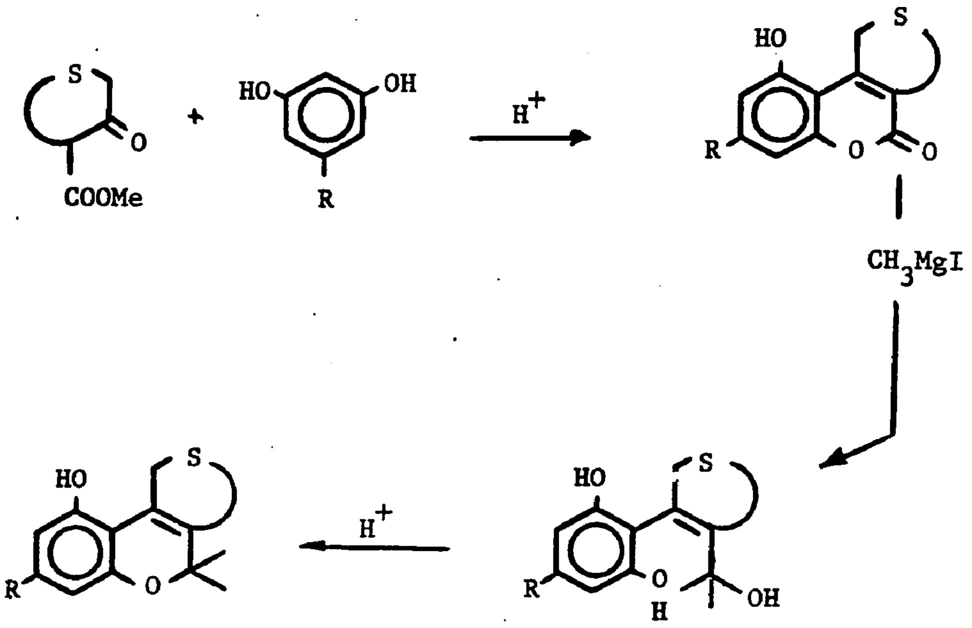
Razdan [41]



Razdan and Handrick [42]

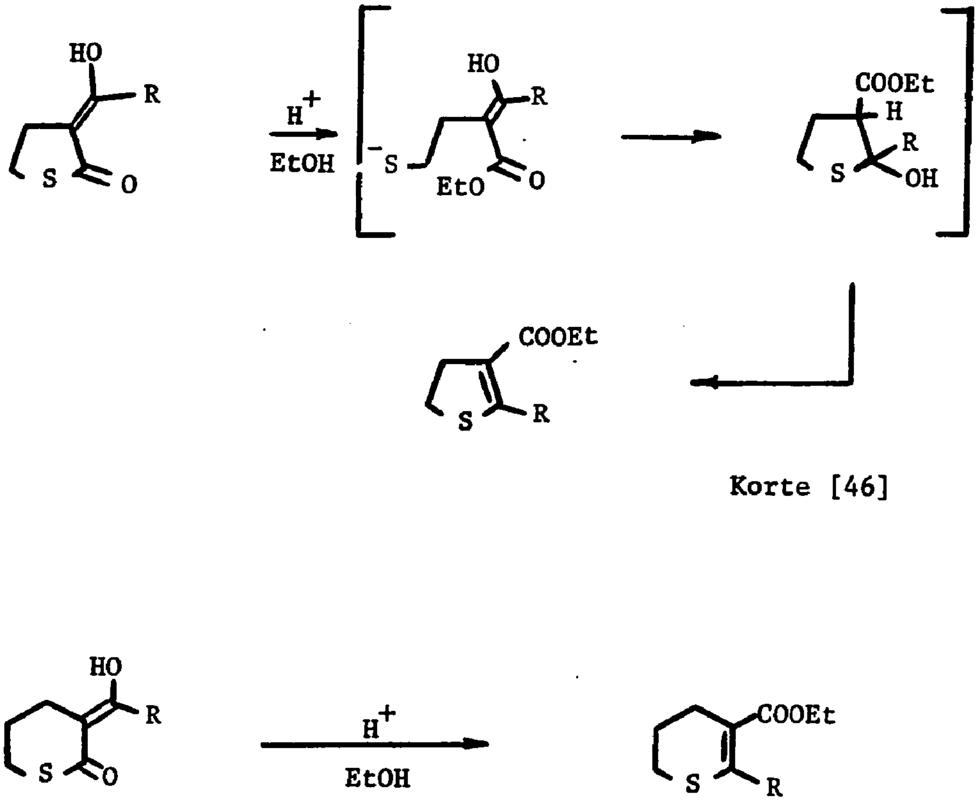
Figure 5

While this approach is useful for the preparation of carbocyclic THC's, it does not lend itself well to the preparation of heterocyclic analogs as the advantage of readily available monoterpeniod starting materials would be lost. An alternate approach to the cannabinoids, based on the Pechmann condensation, was pioneered by Adams in the carbocylic series [7,43], and modified by Razdan [44] in the preparation of heterocyclic THC analogs, the thia-THC's shown in Fig. 4 among them. A generalized scheme to the thia-THC's utilizing this methodology is shown in Scheme I.



Scheme I

Application of this Pechmann condensation strategy to the synthesis of a suitable thieno[3,2-c][1]benzopyran precursor would require the use of a β-carbonyl containing thiolactone functioning as a β-keto ester equivalent. Korte has shown that readily enolizable lactones of this type undergo a facile intramolecular rearrangement, which he termed the acyl-lactone rearrangement [45] (See Scheme II), under conditions similar to those required for the Pechmann condensation.



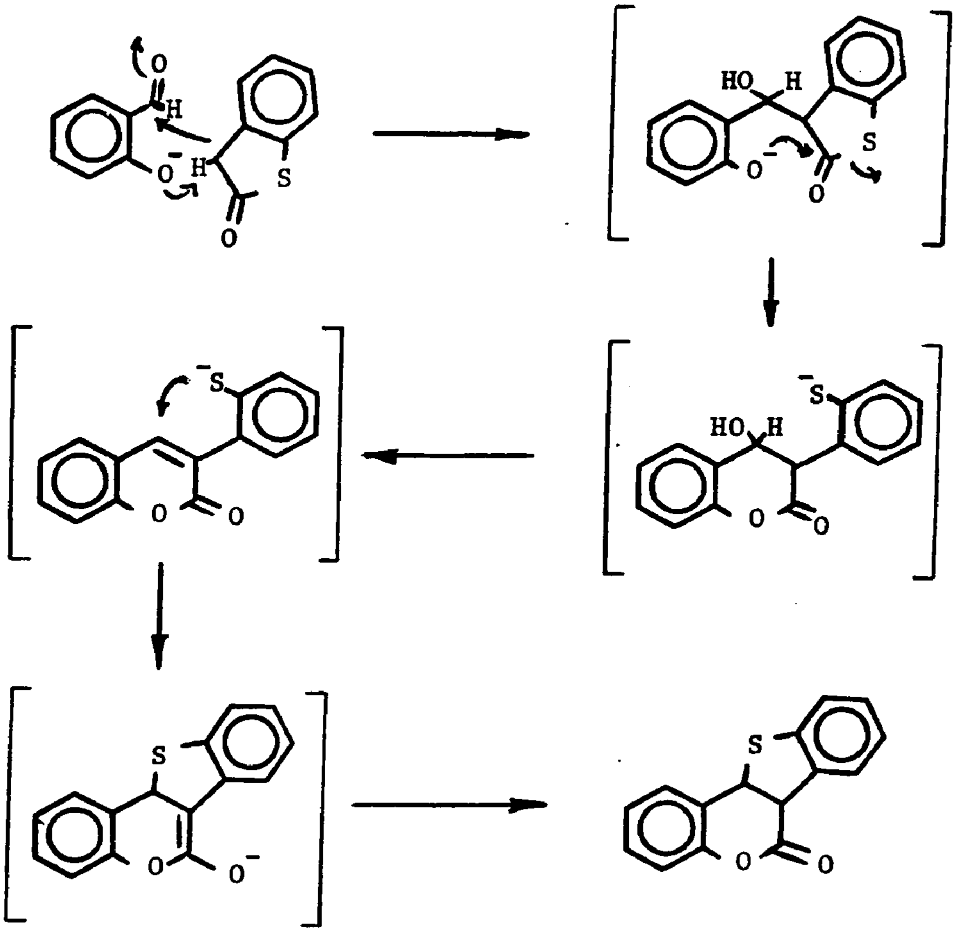
Korte [46]

Korte [47]

Scheme II

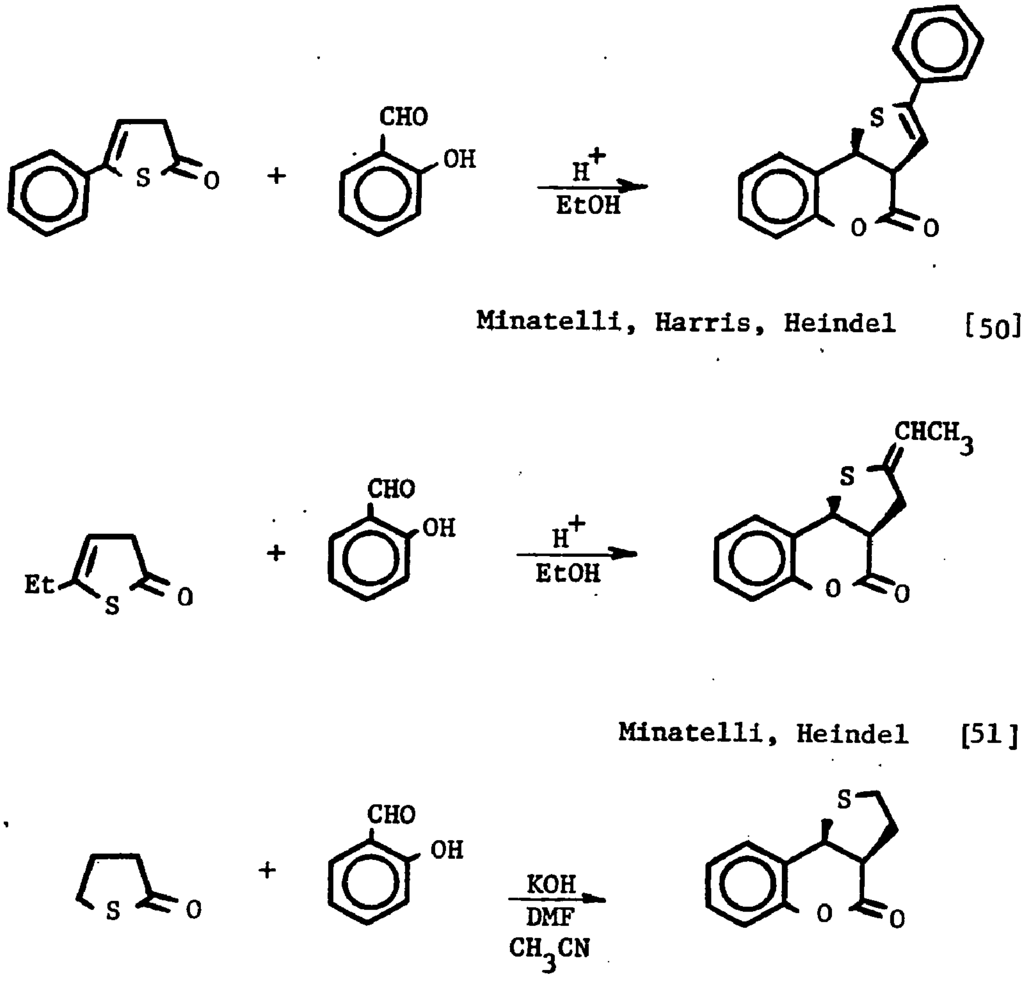
Clearly, an alternate synthetic route would be desirable.

Such a route may be available through the salicylidene-thiolactone rearrangment, a novel condensation-rearrangement reaction of salicyladehydes and thiolactones discovered by Conley and Heindel [48,49]. (See Scheme III).



Scheme III

The generality of this reaction was demonstrated by the work of Minatelli, Harris, Miller, and Heindel, who were able to show that this rearrangment occurred with thiolactones with a wide range of α-proton acidities (see examples below).



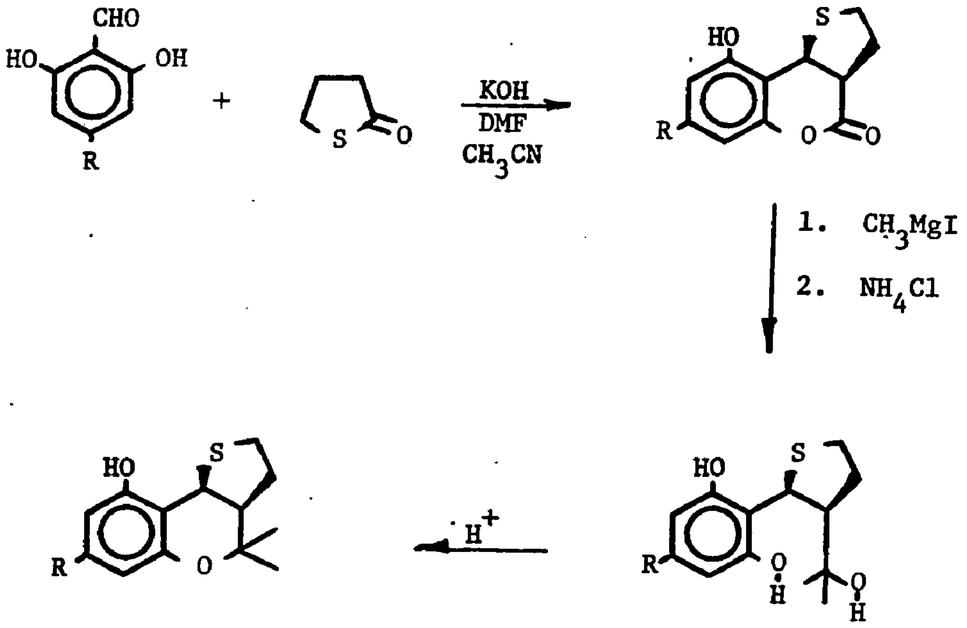
Minatelli, Harris, Heindel [50]

Minatelli, Heindel [51]

Miller, Heindel [52]

Figure 6

The work of Miller appears particularly promising. If the appropriate substituents can be carried through the salicylidene-thiolactone rearrangement, the synthetic strategy outlined in Scheme IV should yield THC analogs with the desired orientation for sulfur.



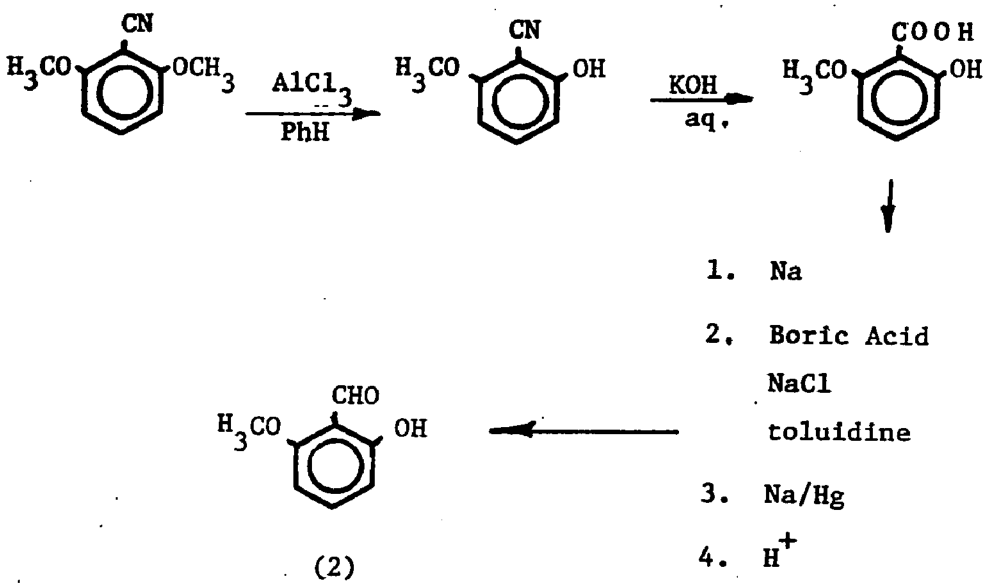
Scheme IV

MODEL STUDIES

Tetrahydrothienolactones.

Initial testing of this proposed synthetic route revolved around the preparation of substituted tetrahydrothienolactones. Although the work of Miller and Heindel demonstrated that substituted salicylaldehydes, when treated with γ-thiobutyrolactone, undergo the salicylidene-thiolactone rearrangement [52], 6-substituted salicylaldehydes and hydroxysalicylaldehydes were not tested. In particular it was anticipated that 6-methoxysalicyaldehyde and 2,6-dihydroxybenzaldehyde might be poor substrates for this rearrangement reaction, as the steric involvement of the di-ortho substituents might impair the susceptibility of the carbonyl group to undergo attack by an enolate anion, even though the sterically induced rotation of the carbonyl moiety out of resonance with the aromatic ring [54], could lead to inductive activation of this group to nucleophilic attack. Similarly, steric problems could arise in the formation of the tetrahydrothieno ring, the result of Michael addition of a thiolate anion occurring at a site proximal to the hydroxy and methoxy substituents.

To test the applicability of the salicylidene-thiolactone rearrangement to these cases, the preparation of 6-methoxysalicylaldehyde (2) and 2,6-dihydroxybenzaldehyde (15) was required. Routes to (2), such as that of Haase [55] (see Figure 7), were circuitous and provided poor yields.



(2)

Figure 7

An alternative to this type of synthesis lies in the mono-demethylation of 2,6-dimethoxybenzaldehyde, readily available from dimethylresorcinol by the method of Wittig [56]. A good analogy is found in the work of Adams, who was able to prepare atranol monomethylether from atranol dimethylether using aluminum chloride in refluxing benzene [57] (see Figure 8). Aluminum chloride has been used by several groups to effect the selective ortho demethylation of polymethoxybenzaldehydes and acylbenzenes [58]. Also widely employed as a reagent for selective ortho demethylation of carbonyl containing aromatics is boron trichloride/methylene chloride [59].

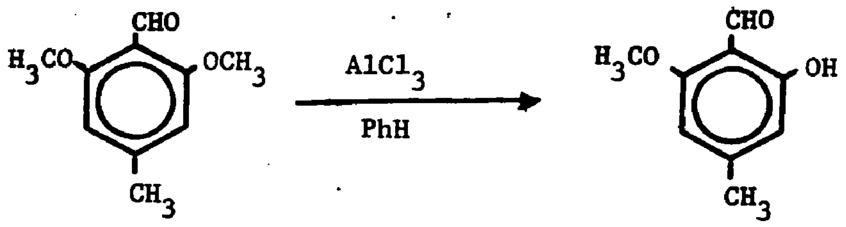
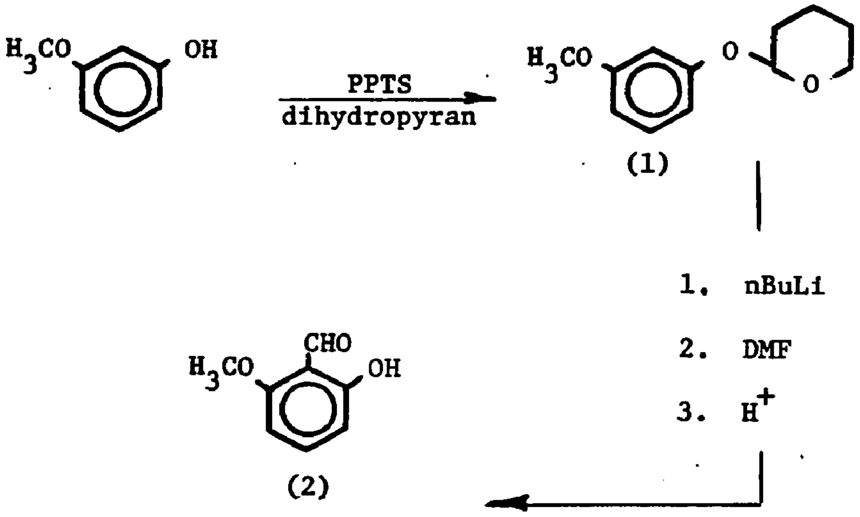


Figure 8

Both of these reagents, however, provided poor yields with 2,6-dimethoxybenzaldehyde as substrate.

A more convenient route to (2) was found in the modification of Wittig's synthesis of 2,6-dimethoxybenzaldehyde, in which one of the methyl ethers was replaced with an acid labile protective group. Thus monomethyl resorcinol was reacted with dihydropyran [60] to give (1) [61]. Treatment with n-butyl-lithium and dimethylformamide, followed by an acidic workup, gave (2) in 47% overall yield (see Scheme V).

Synthesis of 6-Methoxy-2-hydroxybenzaldehyde



SCHEME V

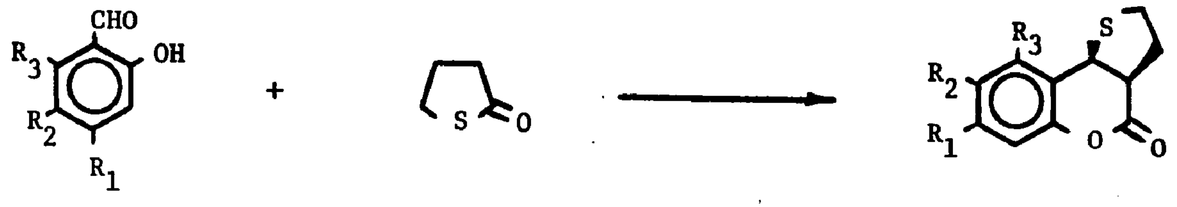
2,6-dihydroxybenzaldehyde, also required for model studies, was prepared by demethylation of 2,6-dimethoxybenzaldehyde *(vide infra)*.

Table 1 summarizes efforts toward the syntheses of the substituted tetrahydrothienolactones (3), all of which were prepared according to the general procedure of Miller and Heindel [53]. The proton NMR spectra of these compounds all showed the characteristic H9b doublet between δ 4.5 and 5.0 ppm, with an approximate coupling constant of 5.5 Hz, suggestive of a *cis* ring fusion. Calculations employing the Karplus equation [62], as modified by Williamson and Johnson [63], gave a dihedral angle between H9b and H3a of approximately 40°, confirming a *cis* ring fusion.

The failure of the dihydroxybenzaldehydes (see Table 1) to undergo the salicylidene-thiolactone rearrangement, while disappointing, was not totally unexpected. The successful rearrangements, utilizing the methoxysalicylaldehydes, to provide (3c) and (3d) suggests that electronic and steric factors were not responsible for this failure. 2,4-Dihydroxybenzaldehyde has been shown to be base-labile [64] and, by analogy, one might expect similar behavior for 2,6-dihydroxybenzaldehyde. In fact, both compounds decomposed upon attempted dissolution in 10% aqueous base. For both of the dihydroxybenzaldehydes, attempted tetrahydrothienocoumarin formation led instead to the formation of a red, resinous material.. Efforts to isolate the desired products (3c) and (3f) or recover the starting dihydroxybenzaldehydes by recrystallization and chromatography were unsuccessful, strongly suggesting that decomposition of the starting materials was the cause of the reaction's failure. Although 2,6-dihydroxybenzaldehyde has undergone a base catalyzed condensation with malonic acid to produce a dihydroxycinnamic acid, good results were obtainable only by the use of a weak base such as aniline [65]. Clearly, a more basic medium is required to generate the enolate of γ-thiobutyrolactone and the requisite dihydroxybenzaldehydes are not stable under these conditions.

Since, however, the methoxy-thienolactones (3c) and (3d) could conceivably be demethylated to provide hydroxythienolactones (3e) and (3f), this route to potential THC analogs was pursued further.

TABLE 1: Synthesis of Tetrahydrothieno[3,3-c][1]benzopyranones.



(3)

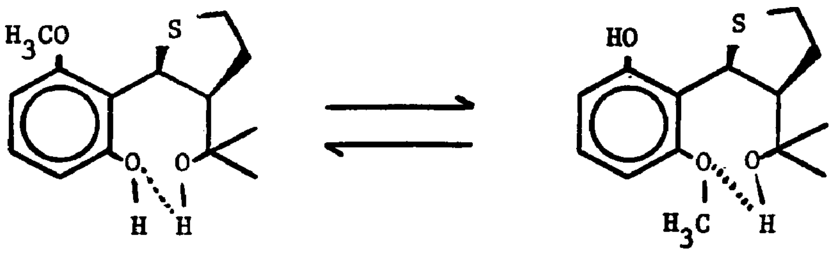
Cmpd.	R_1	R_2	R_3	m.p.	yield	^{1}H NMR data for H9b		Calc. dihedral angle
						Chemical shift	coupling const.	
3a	H	H	H	133-135°C	37%	δ 4.65	5.6 Hz	41.6°
3b	H	Cl	H	146-148°C	25%	δ 4.60	5.6 Hz	41.6°
3c	H	H	OCH_3	138-140°C	37%	δ 4.93	5.8 Hz	40.4°
3d	OCH_3	H	H	134-136°C	12%	δ 4.63	5.4 Hz	42.7°
3e	OH	H	H	--	--	--	--	--
3f	H	H	OH	--	--	--	--	--

Tetrahydrothieno-diols

Classically, dihydrocoumarins have been converted to dialkyl chromans through Grignard addition to form an intermediate phenolic carbinol, which was dehydratively cyclized [66]. The ability to isolate such phenolic carbinol intermediates relates directly to the strength of the acid used in the Grignard work-up; strong acids provided the chroman directly, but ammonium chloride provided the diol [67].

When thienolactones (3) were treated with methyl Grignard in ethereal solution, only moderate yields (∿ 40%) of the diol were obtained, presumably due to poor solubility of the starting material and its magnesium complex. Excellent results were obtained in a mixed benzene/ether solvent system utilizing excess Grignard reagent. Rotary evaporation of the organic phase from the Grignard workup to a minimum volume resulted in the deposition of analytically pure crystals of the phenolic carbinols (4) in approximately 85% yield (results are summarized in Table 2). These high-melting materials all retained a *cis*-substitution pattern at the tetrahydrothiophene ring, as demonstrated by ^{1}H NMR spectroscopy (H2 doublet, $J = 6.0$ Hz, calculated dihedral angle ∿ 39°).

The proton NMR spectrum of one of these compounds, (4c), was unusual in that several protons demonstrated multiple resonances of unequal integral value, i.e., "doublets" appeared at δ 9.5/9.44 and 4.20/4.09, and an "apparent triplet", in fact a pair of doublets with identical coupling constants, appeared centered at δ 5.12. Examination of the ^{13}C NMR spectrum did not show such multiple resonances, but was totally consistent with the assigned structure. It thus appears as if, in solution, (4c) exists as an equilibrium mixture of a pair of H-bonded rotamers, as shown below;

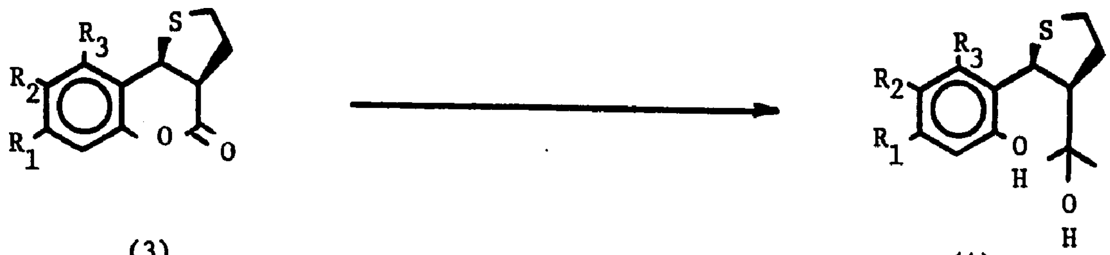


giving rise to double resonances for the phenolic proton, the carbinol proton, and the proton at C2.

Dimethylbenzopyran formation-cyclization of diol (4a).

An attempt to optimize the acid-catalyzed dehydrative cyclization of compounds (4a-d) to the dimethylpyrans was made using compound (4a). Literature routes to dialkylchromans have employed acetic acid/sulfuric acid mixtures to effect cyclization [66], but this method, in the case of (4a),provided low yields of the cyclization products and significant amounts of material

TABLE 2: Preparation of Tetrahydrothienodiols (4a-d).



(3) (4)

Cmpd.	R_1	R_2	R_3	m.p.	Yield	H 2 Chemical Shift	J_{H2-H3}	calc. dihedral angle
4a	H	H	H	192-194°C	86%	δ 4.83	5.9 Hz	39.8°
4b	H	Cl	H	190-192°C	87%	δ 4.77	6.1 Hz	38.6°
4c	H	H	OCH_3	171-173°C	84%	δ 5.12	6.2 Hz	38.1°
4d	OCH_3	H	H	155-156°C	83%	δ 4.74	5.9 Hz	39.8°

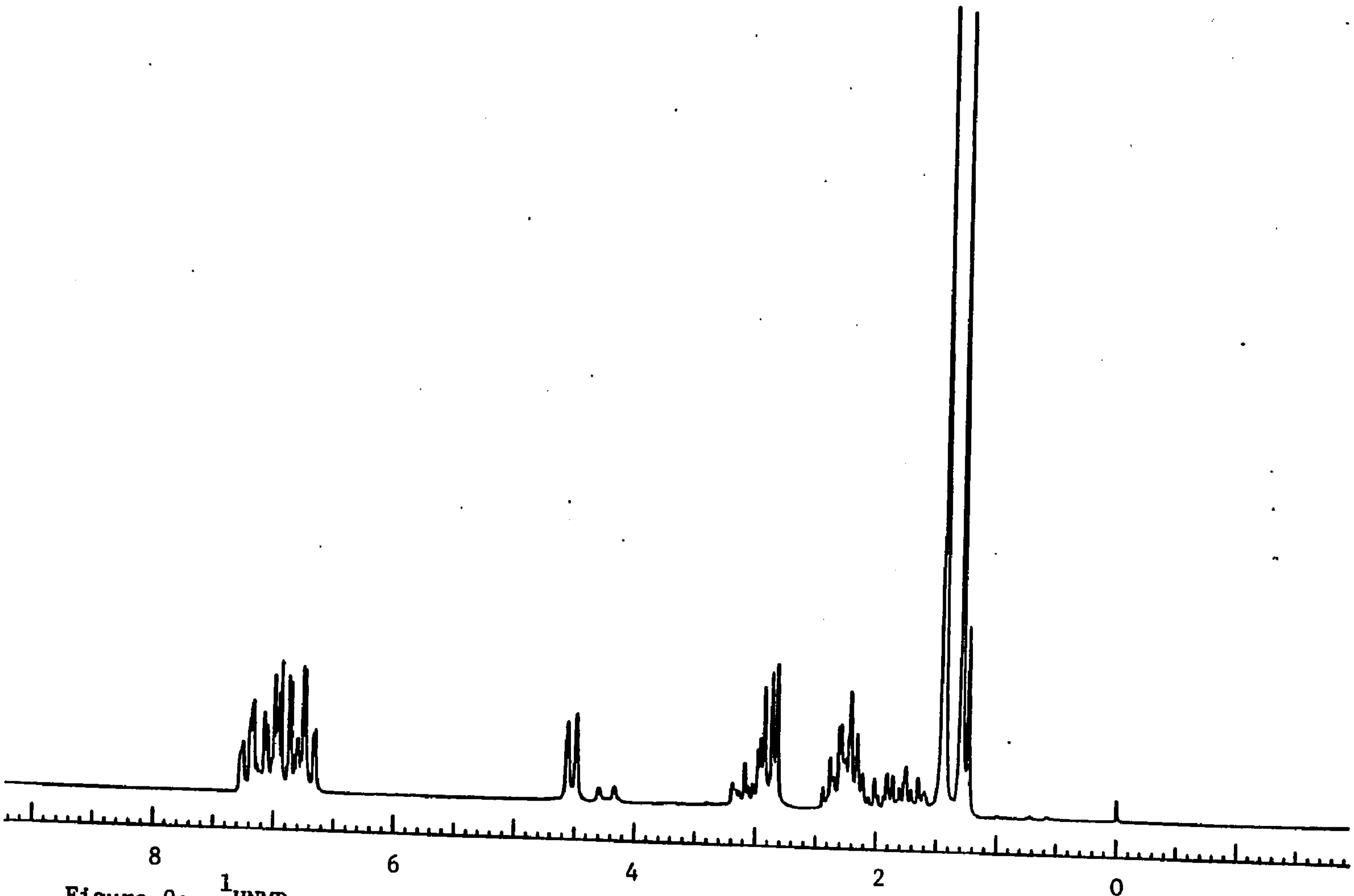


Figure 9: ^{1}HNMR spectrum of *cis* and *trans* 4,4-dimethyl-2,3,3a,9b-tetrahydrothieno-[3,2-c][1]benzopyran.

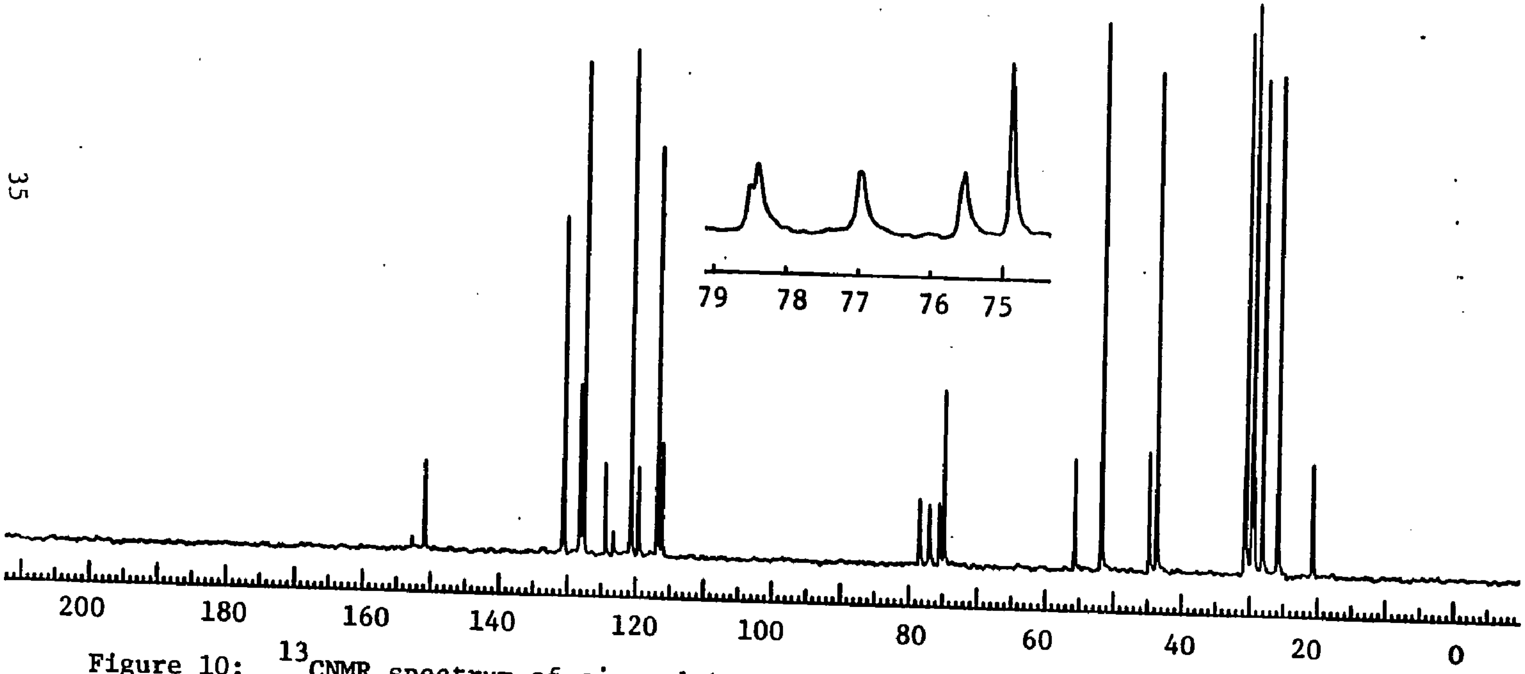


Figure 10: ^{13}CNMR spectrum of *cis* and *trans* 4,4-dimethyl-2,3,3a,9b-tetrahydrothieno-[3,2-c][1]benzopyran.

non-migratory to appropriate TLC systems. Catalytic p-toluenesulfonic acid in refluxing benzene generated similar results. Acceptable yields were obtained with p-toluenesulfonic acid in refluxing methylene chloride, and still better results were obtained in trifluoroacetic acid at room temperature. The latter gave essentially quantitative yields of cyclized material.

In all cases the cyclized material was purified by flash chromatography [68] (TLC - Rf = 0.8, silica, CH_2Cl_2) and the material obtained, homogeneous in several TLC systems of varying polarity, was examined by proton NMR. The spectra obtained were considerably more complex than expected (see Figure 9). Key spectral features include an aromatic region much more complex than that of the starting diol, the appearance of a pair of doublets (of unequal coupling constant and integral value) at a chemical shift expected for the benzylic proton (H9b), and two pair of singlets of unequal integral value at chemical shifts consistent with those expected for the geminal methyl groups of the pyran nucleus. Similarly, the ^{13}C NMR spectrum of this material showed pairs of resonances of unequal intensity for all of the carbons of the suspected product save one (see Figure 10).

Further analysis of the NMR spectral data suggests that the material obtained from the cyclization of 4a was a pair of *cis* and *trans* ring-fused isomers (5). This belief is supported by the ^{1}H NMR coupling constants measured for the H9b protons, with a value of 6.6 Hz being consistent with a *cis* ring fusion and 10.5 Hz with a *trans* [63]. Integration of these doublets defines a 7:3 *cis* to *trans* ratio. Comparison of the suspected C-9b ^{13}C NMR resonances of compounds (5) with those of the ring fusion carbons of *cis* and *trans* decalin show a similar stereochemically induced chemical shift difference [69], but of lesser magnitude due to the greater conformational constraints of the thienobenzopyrans. This same type of correlation is seen when one compares the C-4 ^{13}C NMR chemical shifts of (5) with the C-1 chemical shifts in *cis* and *trans* 2-methylcyclohexanol [70]. These comparisons are summarized in Figure 11.

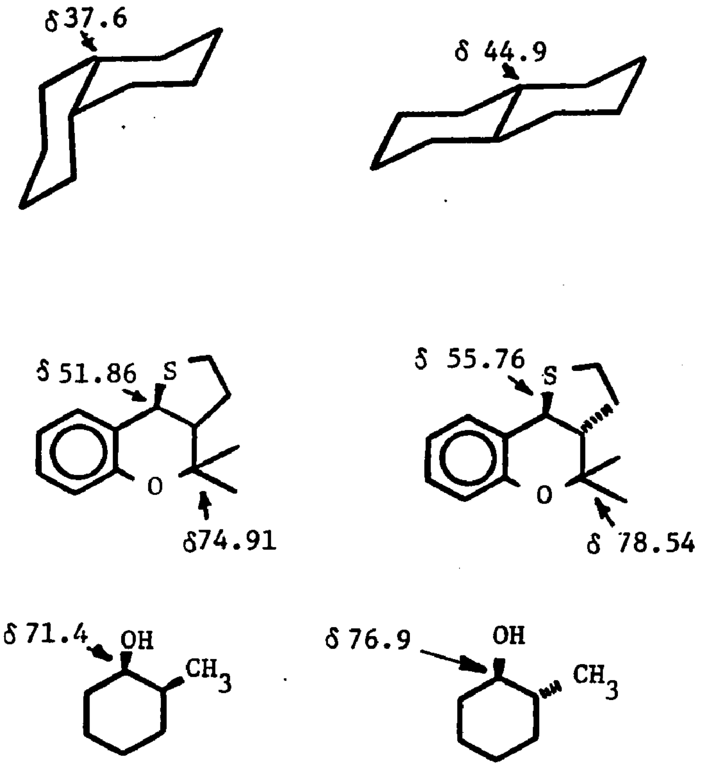
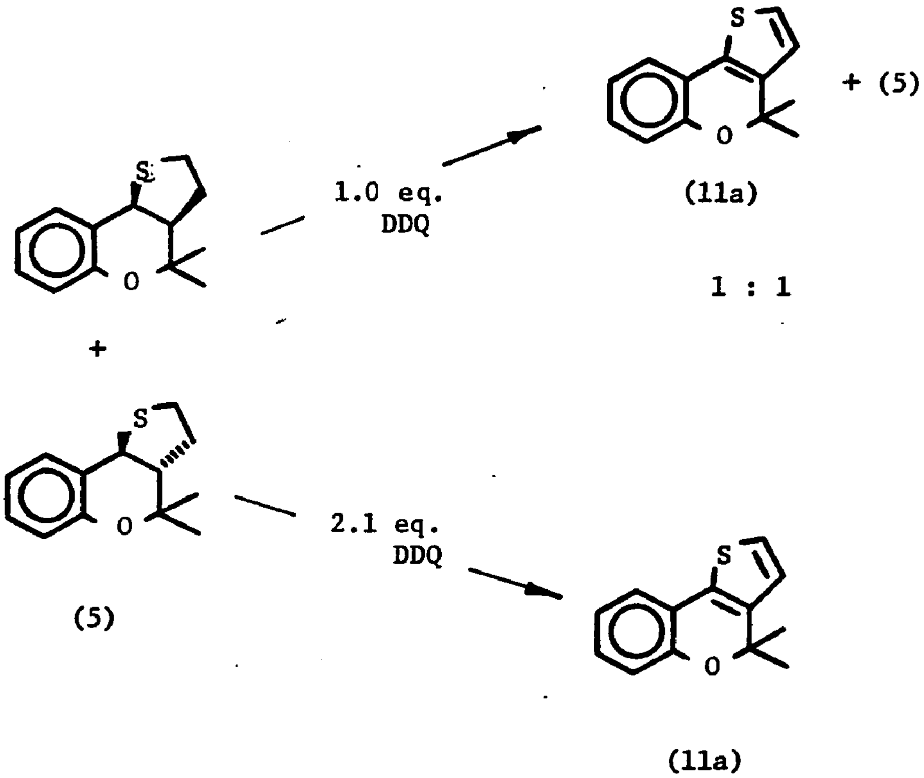


Figure 11

Efforts directed toward the separation of these suspected isomers, i.e., preparative TLC and LC (normal and reverse phase) were unsuccessful, although small quantities of the *cis* isomer could be obtained by crystallization from petroleum ether. The NMR spectra of this material were consistant with the analysis of the mixture given above. GC-MS analysis of this mixture resolved two materials in a 7:3 ratio, whose mass spectra were essentially indistinguishable and fully consistent with the assigned benzopyran structure.

Since physical separation of the isomers appeared possible only by gas chromatography, a chemical conversion of the isomers to a single compound was attempted. Dichlorodicyanobenzoquinone (DDQ) has been used with success for the dehydrogenation of chromans to chromenes [71]. Treatment of the *cis* and *trans* isomer mixture with one equivalent of DDQ in refluxing benzene gave a 45% yield of the fully aromatized 4,4-dimethylthieno[3,2-c][1]benzopyran (11a), rather than the expected dihydrothienobenzopyran. Using 2.1 eq. of DDQ, an 89% yield of (11a) was obtained (see Scheme VI). Since the suspected *cis* isomer comprised only 70% of the mixture of the ring fused isomers (5), this result constitutes proof of the prescence of ring fused isomers.

DDQ OXIDATIONS



Scheme VI

The results obtained above may be rationalized if one considers that the initial tertiary carbonium ion formed by protonation of the carbinol OH may equilibrate with a second tertiary carbonium ion at C-3. Alternately, carbonium ion trapping by the phenolic group could compete with alkene formation, with the alkene subsequently protonated to regenerate a tertiary carbonium ion. In both cases, the stereochemistry at C-3 would be scrambled, allowing for the formation of *trans* ring-fused material (see Figure 12).

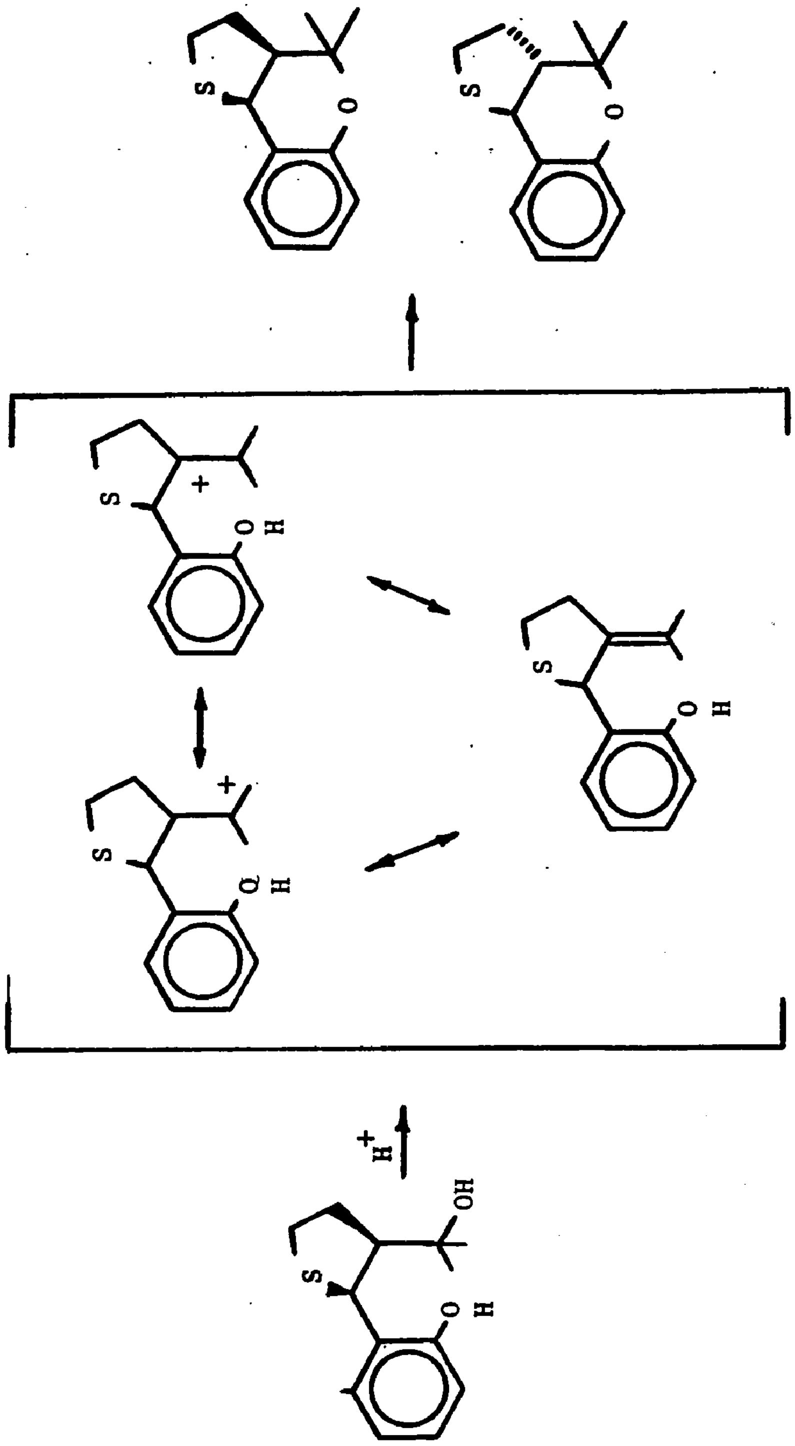


Figure 12

Dimethylbenzopyran formation;cyclization of diols (4b-d).

Cyclization of diol (4b) in trifluoroacetic acid, as in the case of (4a), provided a high yield of the cyclized *cis* and *trans* isomers (6) as the only products. Proton NMR analysis showed 2 benzylic doublets, which when integrated, gave a 4:1 *cis* : *trans* ratio. Dichlorodicyanobenzoquinone dehydrogenation gave chlorothienobenzopyran (11b) in 94% yield.

When methoxydiol (4c) was similarly treated in trifluoroacetic acid, a complex mixture of products was formed in moderate (∿ 55%) overall yield. ^{1}HNMR analysis showed this material to be predominantly the expected isomeric benzopyrans (9). Cyclization in methylene chloride using a catalytic amount of p-toluenesulfonic acid improved the yield (∿ 80%) but did not alter the complexity of the reaction mixture. Purification of this material by successive applications of flash chromatography provided three fractions, the largest of these (72%) being the expected ring-fused isomer (9), with a *cis* to *trans* ratio of 4:1. The other compounds isolated were identified as the phenolic olefin (7) (IR γ 3511, 3432 cm^{-1}; ^{1}HNMR δ 6.02, s, 1H; 1.64, s, 6H; MS, M$^{+\cdot}$ M/z 250 μ 18%), and the thienobenzofuran (8) (^{1}HNMR δ 4.72, s, 1H; 2.15, q., 1H; 1.05, d, 3H; 0.98, d, 3H; MS, M$^{+\cdot}$ 250, intense M-43 M/z 207 9.%). (See Fig. 13).

Dichlorodicyanobenzoquinone oxidation of the mixed isomers (9) gave methoxythienobenzopyran (11c) in 68% yield. The low yield obtained was the result of mechanical losses suffered in handling of the small amount of (9) (68 mg). TLC indicated complete conversion of the isomers (9) to (11c).

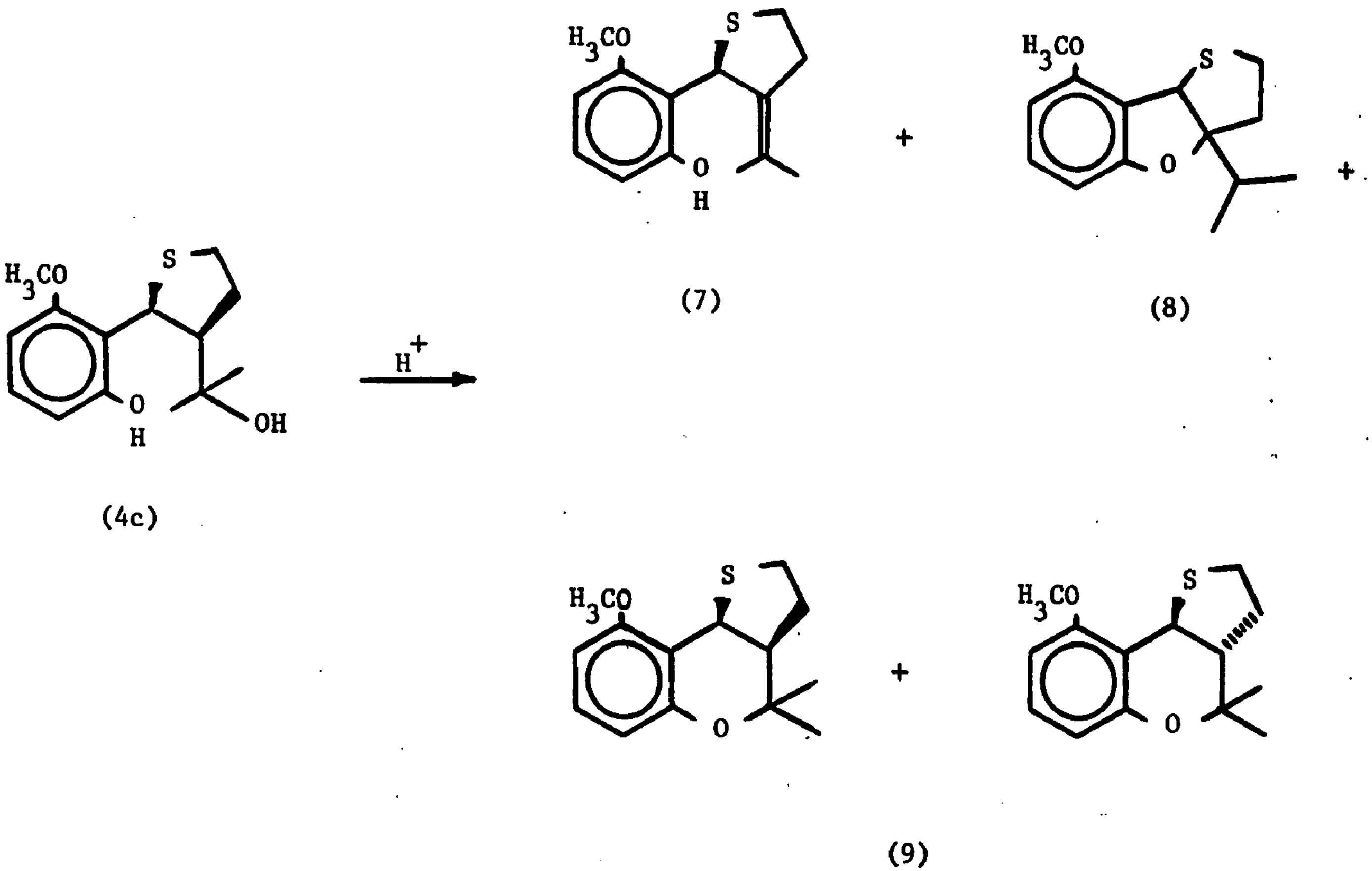


Figure 13

Although the formation of the benzofuran (8) was unexpected, benzofuran formation has been noted proviously in the cannabinoid series. For example, Cardillo condensed menth-3-en-5-ol(A) with orcinol (B) in 5% aqueous citric acid and pulegol (C) with orcinol using p-toluenesulfonic acid in benzene to yield the benzofuran (D) shown in Figure 14 [72]..

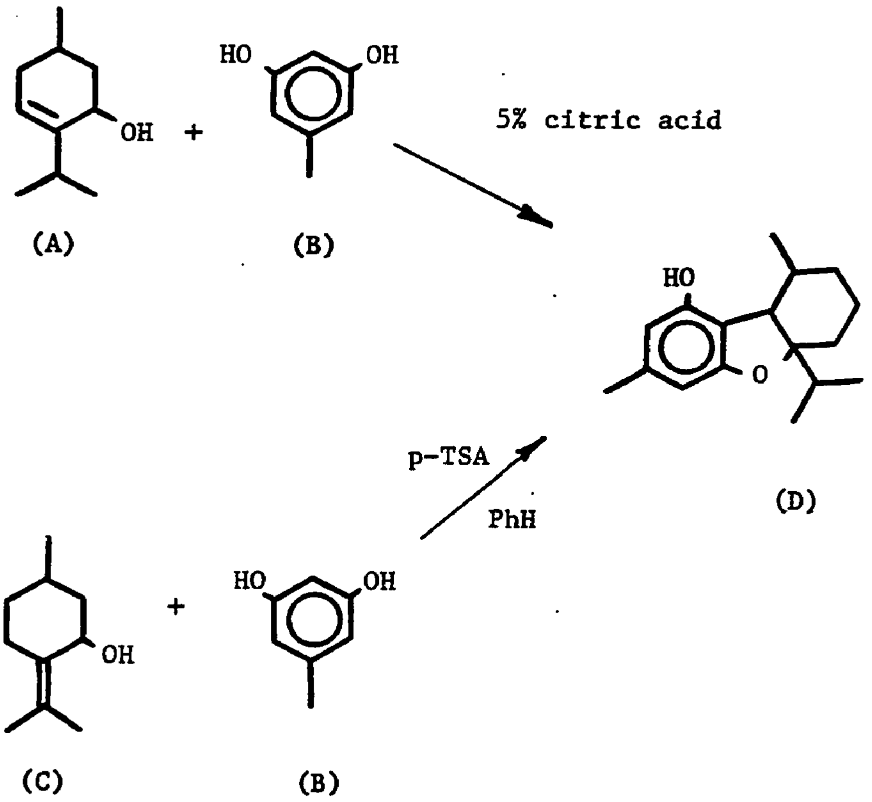


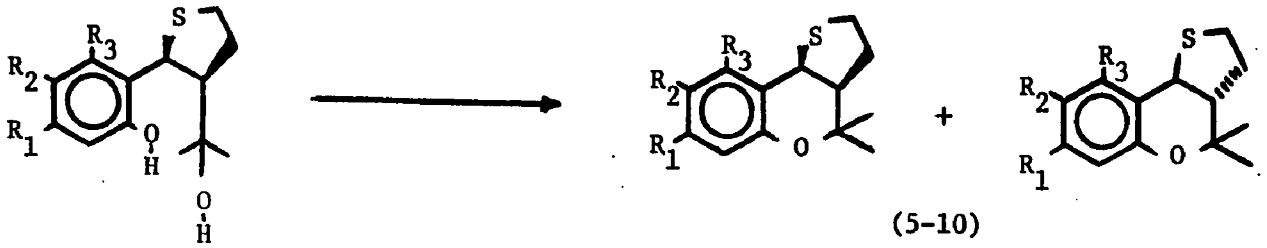
Figure 14

While the appearance of compounds (7) and (8) may be readily rationalized through application of the mechanistic arguments presented in Figure 12, the failure to detect the structural analogs of (7) and (8) in the cyclization of diols (4a) and (4b) is not as easily explained. A steric rationale might be presented, arguing that the steric interactions between the 9-methoxy group and the ring sulfur atom in the benzopyrans (9) could be reduced by the greater separation provided in the benzofuranoid structure (8), and minimized through olefin formation, but the significant amounts of the benzopyrans formed (∿ 60% from SM), coupled with the greater strain expected in a 5-5 vs a 5-6 ring fused system seem to speak against this argument.

It was hoped that the cyclization of methoxy diol (4d) would shed some light on this problem as (4d) has electronic characteristics similar to those of (4c) without presenting the potential steric difficulties. Treatment of (4d) with p-toluenesulfonic acid in refluxing methylene chloride also led to a complex mixture of products, in 85% overall yield. The major component was shown to be the benzopyrans (10) [60%, *cis* to *trans* ratio 4:1, convertible, upon DDQ oxidation, to methoxythienobenzopyran (11d) in 79% yield]. Separation of the other reaction mixture components by preparative TLC, and subsequent ^{1}HNMR analysis failed to reveal evidence for the formation of the structural analogs of compounds (7) and (8). Although this appears to support the steric argument presented, further investigation would be required to advance this hypothesis with any degree of certainty.

The results obtained for the cyclization of diols (4), and the oxidation of the tetrahydrothienobenzopyrans obtained, are summarized in Tables 3 and 4 respectively.

TABLE 3: Synthesis of Tetrahydrothieno[3,2-c][1]benzopyrans.



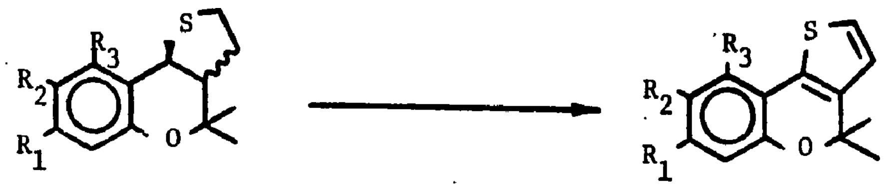
(4)

(5-10)

						^{1}H NMR for H9b		
cmpd.	R_1	R_2	R_3	Method used	yield	*cis* Chemical Shift J value	*trans* Chemical Shift J value	*cis* to *trans* ratio
5	H	H	H	A,B	(A) 86% (B) 99%	δ 4.51 J=6.6 Hz	δ 4.22 J=10.5 Hz	7:3
6	H	Cl	H	B	94%	δ 4.47 J=6.4 Hz	δ 4.19 J=11.4 Hz	4:1
9	H	H	OCH_3	A,B	(A) 80% (B) 58%	δ 4.53 J=7.6 Hz	δ 4.10 J=10.7 Hz	4:1
10	OCH_3	H	H	A	85%	4.49 J=6.3 Hz	4.18 J=11.2 Hz	4:1

Method A: p-TSA,CH_2Cl_2,reflux 8 hrs. Method B: TFA neat, rm. temp. 2 hrs.

TABLE 4: Synthesis of Thieno[3,2-c][1]benzopyrans (11).



(11)

Cmpd.	R_1	R_2	R_3	Rxn. Time	Yield	Analysis
11a	H	H	H	72 hrs	89%	CHS
11b	H	Cl	H	72 hrs	96%	CHS
11c	H	H	OCH_3	24 hrs	68%	CHS
11d	OCH_3	H	H	24 hrs	79%	CHS

9-Hydroxylated model systems.

While the results presented in the previous section of this thesis strongly suggest that a 9-methoxy-7-alkyl-tetrahydrothienobenzopyranone could serve successfully as a precursor to the tetrahydrocannabinol analogs desired, it was reasoned that the use of protective group more labile then an aryl methyl ether would be advantageous as it would, if removed before benzopyran formation is attempted, reduce the steric bulk at the pro-9 center and provide a second phenolic group capable of trapping the tertiary carbonium ion generated. This might lead to a less complex reaction mixture by eliminating the formation of benzofurans and olefinic compounds. A labile protective group would also make it possible to avoid a potentially difficult demethylation reaction as the last step of the reaction sequence. A search for labile protective groups stable to strong bases suggested tetrahydropyranyl ethers and methoxymethyl ethers as the best choices [73]. Thus methods for the preparation of 2,6-dihydroxybenzaldehydes and their selective monoprotection were sought.

Jen, in his preparation of THC analogs, required 2-formylolivetol (2,6-dihydroxy-4-n-pentylbenzaldehyde), which he claimed to have prepared by a Gatterman formylation (Adam's modification) of olivetol [74]. This ortho-formylation is unusual in that it generally occurs only when positions para to the phenolic group are blocked [75]. In fact, the work of Hendrick [76] and Luteyn [77] confirm that the actual product of this reaction is the normal

Gatterman product, 2,4-dihydroxy-6-n-pentylbenzaldehyde (See Figure 15).

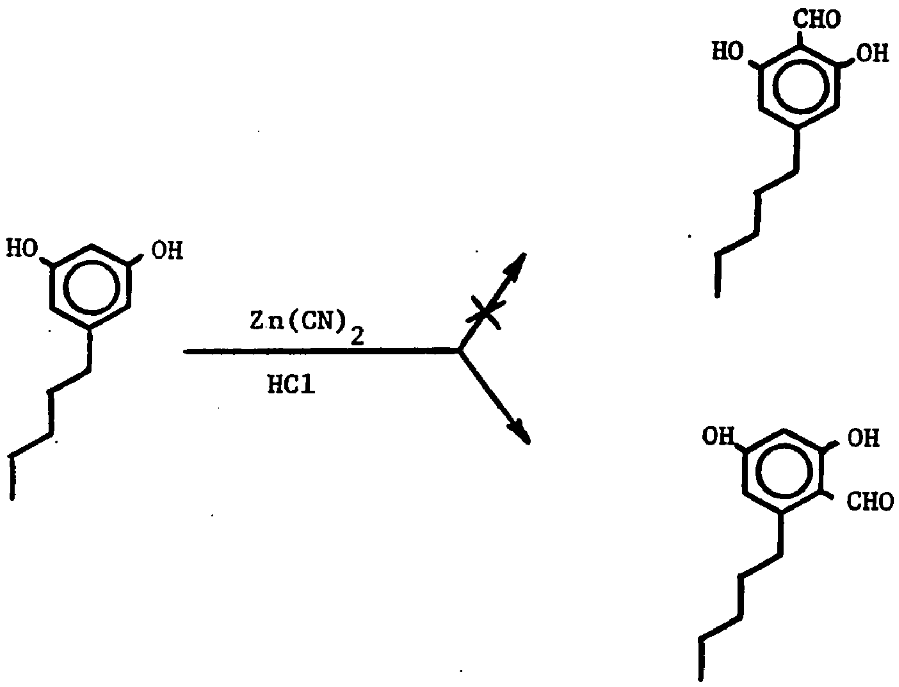


Figure 15

Castagnoli was able to prepare 2-formylolivetol from olivetol dimethyl ether using Wittig's chemistry [56] to provide the 2,6-dimethoxybenzaldehyde, which was subsequently demethylated with aluminum bromide in carbon disulfide [78], with the demethylation proceeding in 38% yield. Using this same methodology, Adams was able to demethylate atranol dimethylether and 2,6-dimethoxybenzaldehyde in 70% and 78% yields respectively [57,65]. A search for a better method of demethylation was undertaken, using 2,6-dimethoxybenzaldehyde (12) as a model [56]. Boron tribromide in methylene chloride [79] gave 2,6-dihydroxybenzaldehyde (13) in 15% yield, the best obtained for the procedures attempted, which included demethylation in hydrogen bromide/acetic acid and the use of sodium-para-thiocresolate/hexamethylphosphoramide in refluxing toluene [80]. Since Adam's yield of (13) was reproducible, it was decided to use the aluminum bromide/carbon disulfide demethylation procedure, despite the low yields obtained by Castagnoli [78].

Although a method for the monoprotection of 2,6-dihydroxybenzaldehyde was not available in the literature, 2,2'-dihydroxybenzophenone has been mono-methoxymethylated by an acid catalyzed acetal exchange with dimethoxymethane. Under identical conditions, o-hydroxyacetophenone did not react [81] (See Figure 16). 2,4-dihydroxybenzaldehyde, dissolved in dihydropyran containing a catalytic amount of p-TSA, gave only the 4-tetrahydropyranyl ether [82] (see Figure 16).

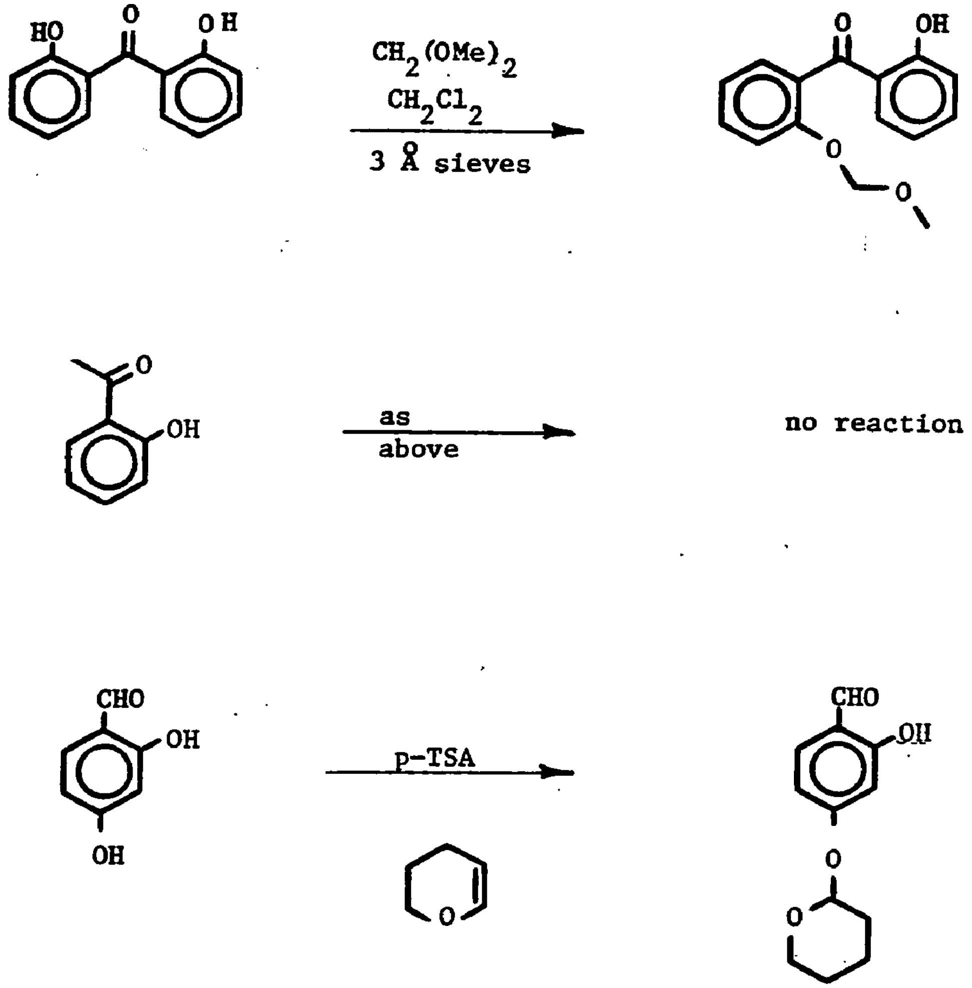


Figure 16

These results may be explained through the intramolecular hydrogen bonding of the ortho phenolic group to the carbonyl oxygen, thereby reducing the nucleophilicity of this moiety (see Figure 17).

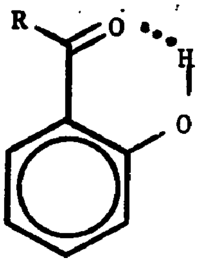


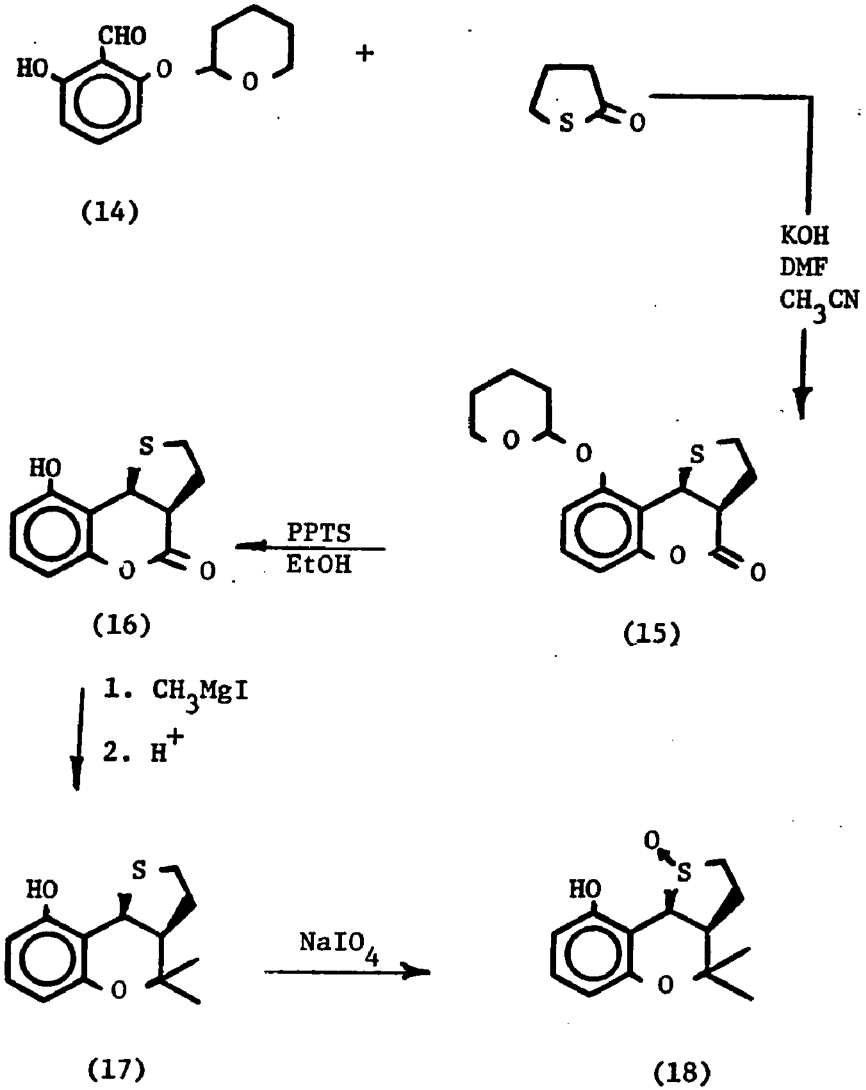
Figure 17

Since only one of the phenolic OH's of the symmetrical 2,6-dihydroxy-4-alkylbenzaldehydes could form this intramolecular hydrogen bond at any given time, monoprotection of these compounds should be possible. Using 2,6-dihydroxybenzaldehyde, methoxymethylation according to Yardley and Fletcher [81] returned only polymer, but tetrahydropyranylation (dihydropyran, pyridinium tosylate, methylene chloride, 3 hr. reflux) gave tetrahydropyranyloxysalicylaldehyde (14) in 81% yield.

The tetrahydropyranylated salicylaldehyde (14) reacted smoothly with γ-thiobutyrolactone under salicylidene-thiolactone rearrangement conditions to give the tetrahydropyranyloxythienolactone (15) which was deprotected (pyridinium tosylate, ethanol, 55%, 8 hrs.) in excellent yield to give the hydroxythienolactone (16). Treatment of (16) with excess methyl Grignard reagent (∿ 10 eq.) resulted in only partial conversion to the desired phenolic carbinol, presumably due to the poor solubility of the Grignard salt of (16) in the mixed ether/benzene solvent system.

Since literature precedent suggested that, once a long alkyl chain was incorporated into the structure, solubility in ether/benzene would no longer be a problem [36,37], the crude reaction mixture was treated under cyclization conditions (p-toluenesulfonic acid, methylene chloride, reflux) with the cyclized material separated from unreacted (16) by flash chromatography. The cyclized material was obtained as an oil (60% corrected for recovered starting material) which was crystallized from methanol to give the hydroxybenzopyran (17) as a pure *cis* isomer (^{1}H NMR δ 4.41, d, J = 7.9 Hz, 1H). Periodate oxidation [83] of (17) gave sulfoxide (18). The above results are summarized in Scheme VII.

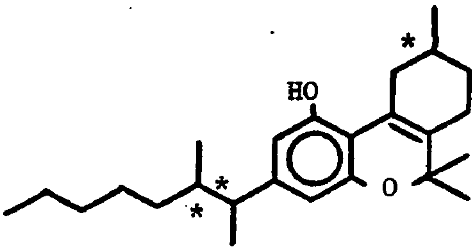
Preparation of a Model 9-Hydroxylated THC Analog



Scheme VII

THC analogs - incorporation of an aliphatic side chain

Adaptation of the synthetic strategy discussed in the previous sections to the preparation of THC analogs suitable for biological testing requires the introduction of a lipophilic side chain at C7. A review of the side chain related SAR studies of Adams [7], Razdan [37], and Milne and Johnson [19], suggests that several branched alkyl, aralkyl, and aralkyloxy groups possessing an extended chain length approximately equal to that of n-heptyl, provide optimal THC activity. Of these, the 1,2-dimethylheptyl side chain has generated the greatest amount of interest, and has been used in the preparation of several highly active THC analogs including Adam's dimethylheptylpyran (DMHP)[7], a mixture of 4 pairs of diastereomers with only the (-) threo isomers demonstrating activity [84]. Although the use of threo-1,2-dimethylheptylresorcinol, whose selective preparation has been described [85], would hold great promise for optimizing the potential activity of a new THC analog, it was decided that, in initial studies, the incorporation of an

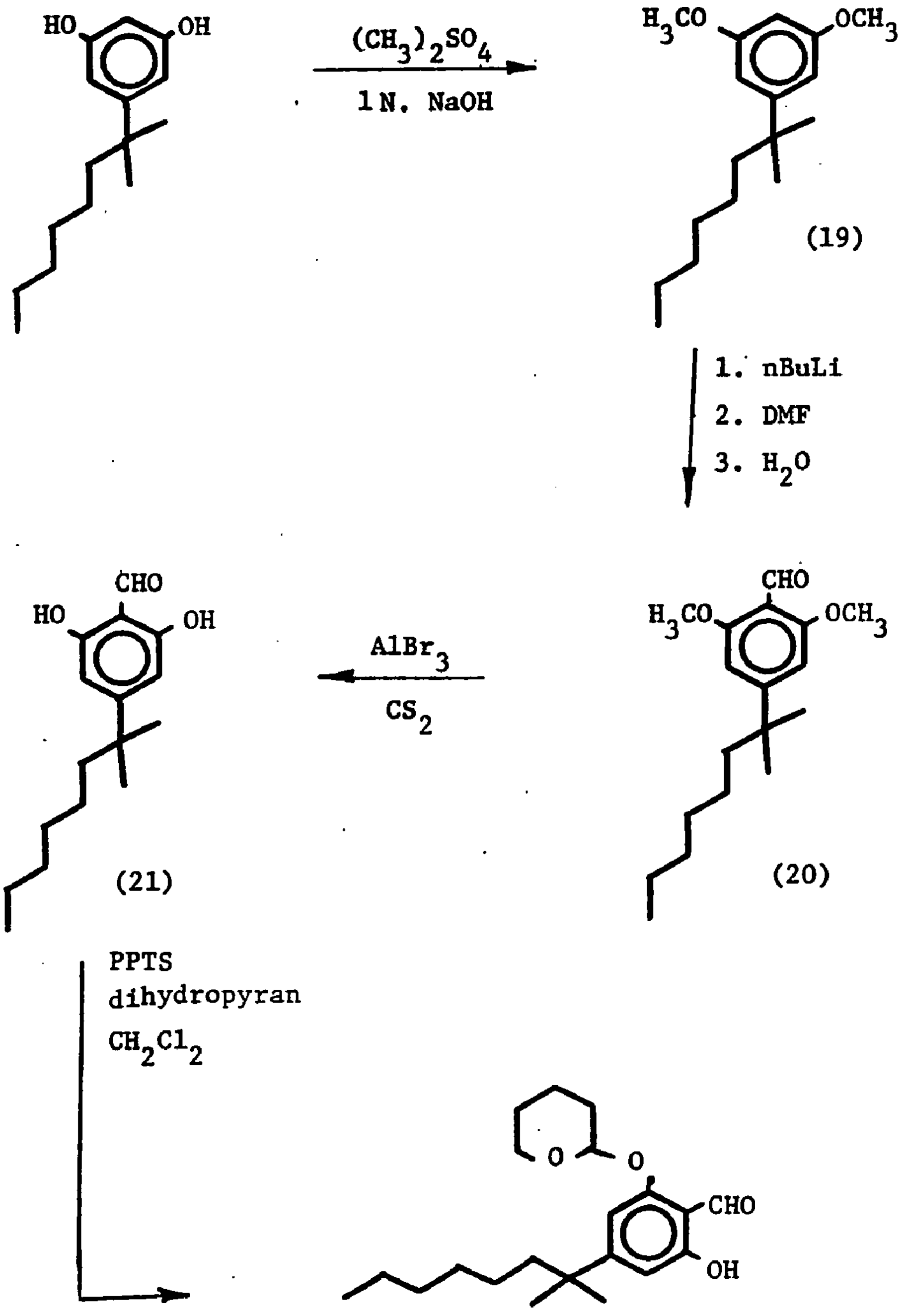


DMHP

achiral side chain would be preferable. The most appropriate choice then becomes the 1,1-dimethylheptyl side chain which, in the analgetic SAR studies of Milne and Johnson [19], provided THC analogs equipotent with those bearing the 1,2-dimethylheptyl side chain (as a mixture of erythro and threo isomers).

Thus, 1,1-dimethylheptyl resorcinol [86,87,43] was treated with dimethylsulfate to yield the dimethylether (19). Formylation of (19), using the method of Wittig as modified by Townsend [88], gave dimethoxybenzaldehyde (20), which was separated from unreacted (19) by flash chromatography. Aluminum bromide demethylation of (20) provided 2,6-dihydroxybenzaldehyde (21) as a yellow oil. The excellent yield of (21) obtained (96%) is in sharp contrast with the 38% yield of formylolivetol obtained by Castagnoli [78] using the same methodology. The demethylation procedure, as described by Adams [65] for the preparation of 2,6-dihydroxybenzaldehyde, entails decantation of the carbon disulfide from the formed aluminum complex of the dihydroxy product, which cakes to the sides of the reaction vessel. Reaction of (20) gave a carbon disulfide soluble aluminum complex requiring the isolation of this complex by rotary evaporation of the CS_2 solvent. Presumably, the aluminum complex of 2-formylolivetol, although seen to precipitate from carbon disulfide upon the addition 2-formylolivetol dimethylether to the reaction medium, shows considerable solubility in carbon disulfide, and the yield of this compound could be improved by working up the otherwise discarded carbon disulfide layer.

Unfortunately, compound (21) turned red upon exposure to air; a possible suggestion of air-oxidation. Although ^1H NMR and ^{13}C NMR spectroscopy did not reveal the presence of impurities, the semicarbazone of (21) was prepared for the purpose of elemental analysis, and the rest of this material was immediately converted to its tetrahydropyranyl ether (22), which was stable enough to store for at least several weeks. (See Scheme VIII for a summary of synthetic efforts).


HO
OH
$(CH_3)_2SO_4$
1N. NaOH
H_3CO
OCH_3
(19)
1. nBuLi
2. DMF
3. H_2O
CHO
HO
OH
$AlBr_3$
CS_2
CHO
H_3CO
OCH_3
(21)
(20)
PPTS
dihydropyran
CH_2Cl_2
O
O
CHO
OH
(22)

Scheme VIII

Reaction of (22) with γ-thiobutyrolactone under the standard conditions used for the salicylidene-thiolactone rearrangement gave, following chromatographic workup, a crude oil whose ^{1}H NMR spectrum did not demonstrate the benzylic doublet (H9b) characteristic of the tetrahydrothieno[3,2-c][1]benzopyran-4-ones. The presence of a singlet, integrating for one proton, at δ 7.9 and a multiplet worth four protons at δ 3.0 suggested that either the coumarinic ethyl mercaptan or disulfide was formed (see Figure 18). Attempted purification of this crude material by preparative TLC for purposes of identification returned an oil which,by analytical TLC using the same solvent system used in its separation, was shown to be a mixture of at least three compounds. Proceeding on the assumption, buttressed by ^{1}H NMR spectroscopy, that these compounds were formed by partial loss of the THP protective groups from the disulfide shown in Figure 18, the crude oil from the attempted salicylidene-thiolactone rearrangement was treated with pyridinium tosylate in ethanol to effect deprotection. The single solid material obtained was shown to be disulfide (23)(see Scheme IX, p. 64).

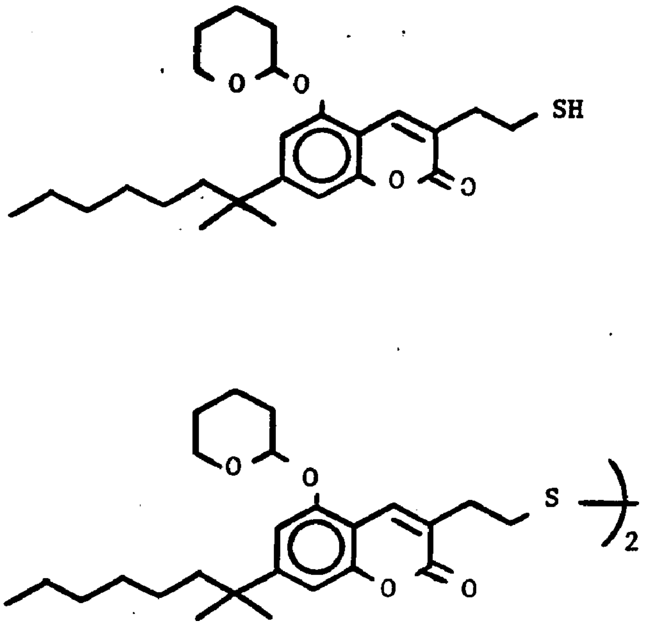


Figure 18

While a reason for the unfavorable oxidation - Michael addition competition-demonstrated in this case is unclear, it is apparent that an oxygen-free reaction medium is necessary if the thienolactone from (22) is to be prepared. An observation made by Stevens in his preparation of chiral steroid intermediates [89] suggested that further modifications of the conditions for the salicylidene-thiolactone rearrangement might be in order. Alkylation of 9-iodocamphor with sodio-dimethylmalonate in dimethylformamide at 100°C led to the formation of a complex reaction mixture from which the desired ketoester (B) could be obtained in only 40% yield (see Figure 19).

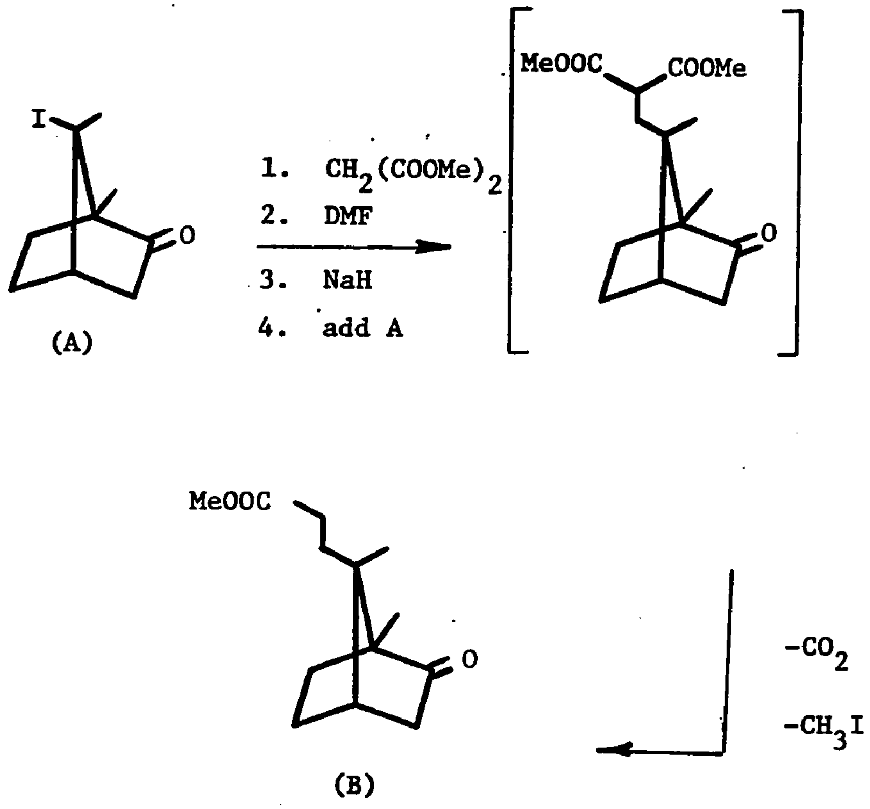
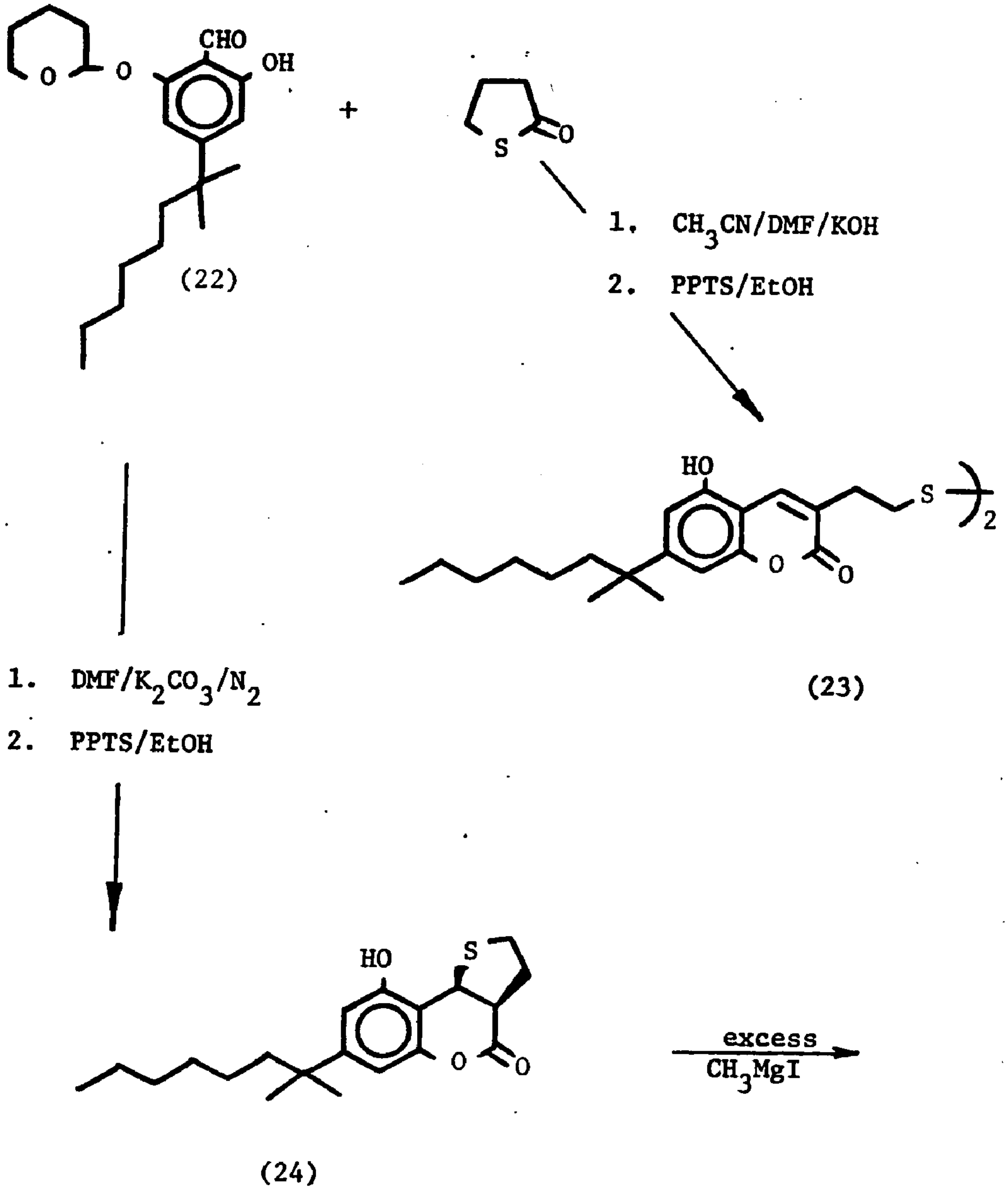


Figure 19

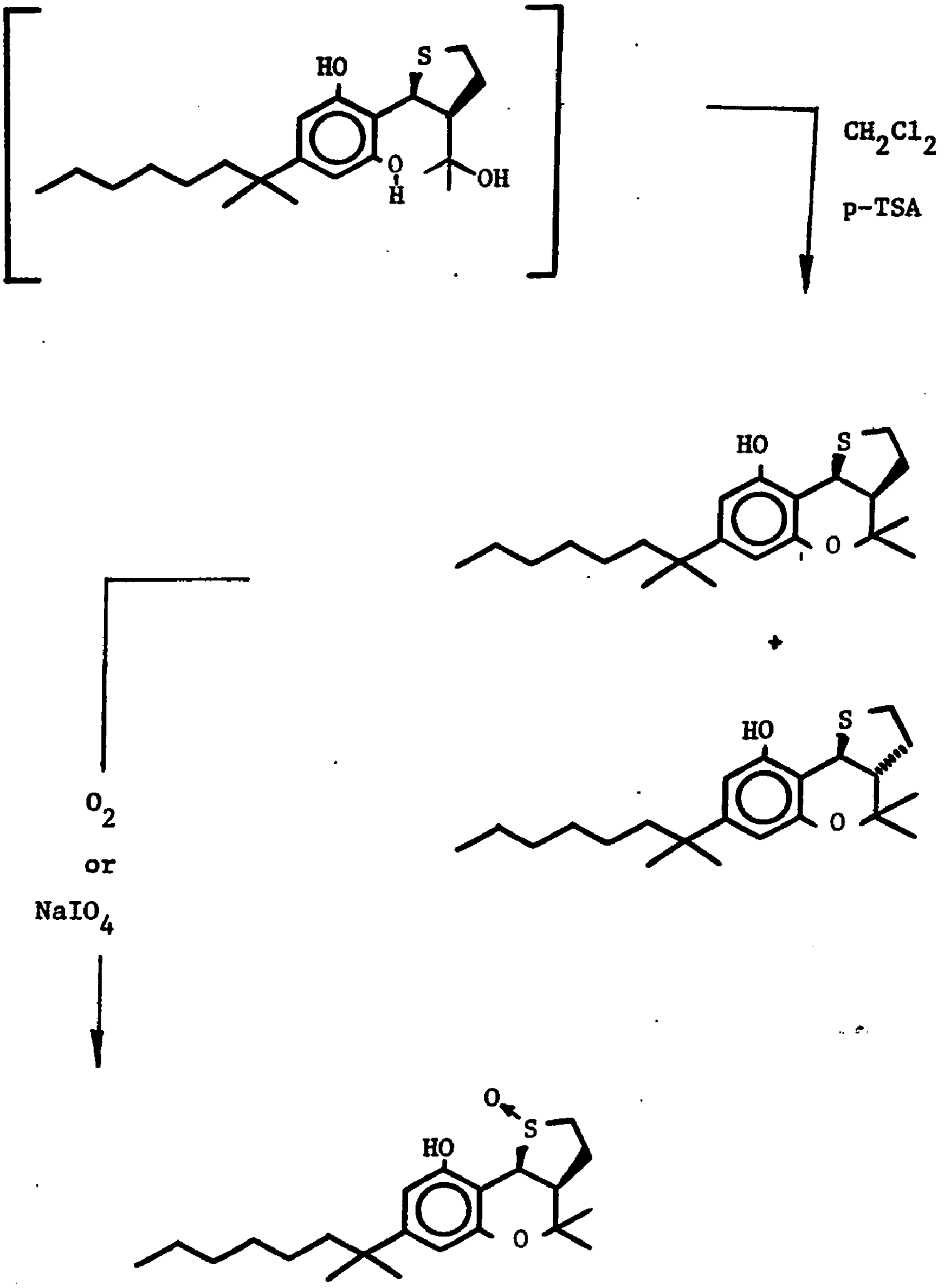
Noting that, even at room temperature, DMF is known to decompose in the presence of bases such as potassium hydroxide, sodium hydroxide, or calcium hydride to give carbon monoxide and dimethylamine [90], and that the sodio-malonate used was formed by the addition of methylmalonate to a DMF/NaH suspension, Stevens inferred that the complex reaction mixture and low yields of (B) obtained were the result of the presence of the competing nucleophile, dimethylamine. Substitution of potassium carbonate as the base used to generate the malonate anion led to markedly improved yields of (B). Since thioesters are known to react readily with nucleophiles to generate the free thiolate [91], use of Steven's modification appeared appropriate. Similarly, the isolation of a small amount of ω-thiobutyric acid disulfide from the reaction mixture that gave disulfide (23) suggested that water should also be eliminated.

Accordingly, equimolar portions of (22) and γ-thiobutyrolactone were dissolved in dry dimethylformamide, which was then purged with nitrogen for 0.5 hours by the direct introduction of the gas into the reaction mixture. Anhydrous potassium carbonate was added, and the reaction mixture was stirred at 80°C under nitrogen. This modification gave a crude product which, by ^{1}H NMR, appeared to be a mixture of the THP-protected thienolactone and a small amount of the THP-protected disulfide (23) [sulfide to disulfide ratio ∿ 5:1, ^{1}H NMR integration of the aromatic resonances δ 7.8 (C4′ disulfide), 6.9/6.4 (pr of d, ArH, disulfide), 6.8/6.6 (pr of d, ArH, sulfide) 5.5/5.3 (pr of br. s, acetal H's). 4.8 (d, H9b, sulfide)]. Removal of the THP-groups [60], followed by chromatography [92], gave hydroxythienolactone (24) in 42% yield from (22).

Treatment of (24) with approximately 10 equivalents of methyl Grignard gave the crude phenolic carbinol in essentially quantitative yield. Since purification of this oil would most likely have resulted in dehydration and/or cyclization, this crude material was dried by the azeotropic removal of water (methylene chloride), dissolved in dry methylene chloride containing p-toluenesulfonic acid, and cyclized to give a golden oil (67%) that, by ^{1}H NMR, was shown to be primarily a mixture of the *cis* and *trans* tetrahydrothienobenzopyrans (25)(9:1 *cis* to *trans* by integration of the H9b resonances). All attempts to purify this material by chromatographic means were unsuccessful, but attemptee crystallization of this oil from ether/petroleum ether led to the isolation of a white cyrstalline solid from the then red solution. Chromatography of this material (chloroform/methanol, 19:1) returned a small amount of pure *cis* (25) and a new material whose ^{1}H NMR spectrum retained the H9b doublet, but showed considerable broadening of the ring methylene resonances. ^{13}C NMR showed a new resonance at δ 64.16, which suggested that a change in the environment of C9b had occurred. Mass spectral evidence ($M^{+\cdot}$ M/z 378 vs. M/z 362 for compd. (25), major fragment at M-63, corresponding to the loss of $\cdot CH_2\underbrace{-S=O}_{H}$) allows the assignment of this compound as the tetrahydrothienobenzopyran-S-oxide (26). Further attemps to prepare and purify (25) led to the same oxidation problems, but direct oxidation of the crude sulfide product with sodium periodate [83] gave a sulfoxide indistinguishable by ^{1}H NMR from the air oxidation product (26). These results are summarized in Scheme IX.


CHO
OH
O
O
+
S
O
(22)
1. $CH_3CN/DMF/KOH$
2. PPTS/EtOH
HO
S
2
O
O
(23)
1. $DMF/K_2CO_3/N_2$
2. PPTS/EtOH
HO
S
O
O
(24)
excess
CH_3MgI

SCHEME IX



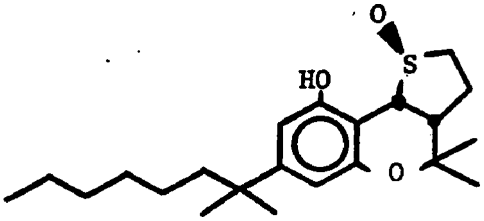
(25)

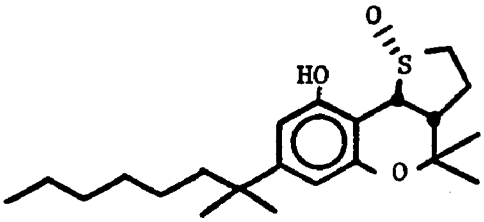
(26)

Scheme IX (Continued)

Sulfoxide (26) - Chirality at Sulfur.

Since sulfoxides, by virtue of their tetrahedral configuration at sulfur, are chiral [93], one might expect that oxidation of the racemic sulfide (25) would provide the corresponding sulfoxide as a mixture of diastereomers. Examination of the ^{1}H NMR spectrum of (26)does not support this supposition, as only one benzylic doublet for H9b is seen. A more definitive test can be found in ^{13}C NMR spectroscopy, which is particularly sensitive to conformational differences such as the ones likely to be seen in the diasteromeric sulfoxides shown below [94]. While some overlap of the



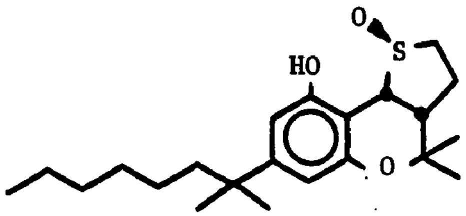


^{13}C resonances might reasonably be expected for these compounds, some differences should be noted, particularly at C9b. The apparent lack of multiple resonances throughout the ^{13}C spectrum of (26) suggested that (25) had essentially oxidized chirally. Such preferential oxidation of chiral sulfides has been previously noted in the penicillin series [95].

Determination of the relative chirality at sulfur becomes important when considering whether or not sulfoxide (26) adequately mimics the structure of hexahydrocannabinol. The use of aromatic solvent induced shifts (ASIS) in proton NMR spectroscopy has provided a simple method for the determination of the chirality at sulfur in similar systems [96]. Although the precise nature of the interaction between aromatic solvents and the polar functional groups of the substrate remains unknown, a model put forth by Ledaal [97] has been successfully applied to the determination of relative stereochemistry by NMR. Ledaal suggests that the six-fold axis of symmetry of benzene aligns with the positive end of the functional group dipole, forming a collision complex. If this is the case, protons on carbons proximal to the polar functionality and anti to it should experience an anisotropic shift(relative to an inert solvent)induced by the aromatic solvent. Such shifts should be minimal or non-existent for syn protons. Each polar functional group in a given molecule is capable of forming a collision complex.

In order to be certain that the ^{1}H NMR chemical shift differences noted for sulfoxide (26) were indeed due to ASIS effect at the sulfoxide group, ^{1}H NMR spectra in deuterochloroform and hexadeteurobenzene were obtained for sulfide (25) and sulfoxide (26). Subtraction of the shifts noted for (25) from those noted for (26) demonstrated that the sulfoxide oxygen is syn to the benzylic proton H9b (see Table 5). Examination of molecular models shows that this sulfoxide isomer provides better overlap with hexahydrocannabinol (HHC) than does the isomer with H9b and the sulfoxide oxygen anti.

TABLE 5: ASIS Determination of Relative Chirality at Sulfur: Compound (26).



Proton(s)	Chemical Shift δ $CDCl_3$ Sulfoxide (26)	Sulfide (25)	Chemical Shift δ C_6D_6 Sulfoxide	Sulfide	Δ Sulfoxide	Δ Sulfide	Δ Sulfoxide-sulfide
H9b	4.41	4.48	4.44	4.48	-0.03	0.00	-0.03
αCH_3	1.43	1.45	1.00	-1.20	0.43	0.25	+0.18
βCH_3	1.28	1.31	0.94	0.98	0.34	0.34	+0.01
αH2	3.45	2.98	2.75	2.50	0.70	0.70	+0.22
β H2	2.90	2.89	2.40	2.45	0.50	0.49	+0.01

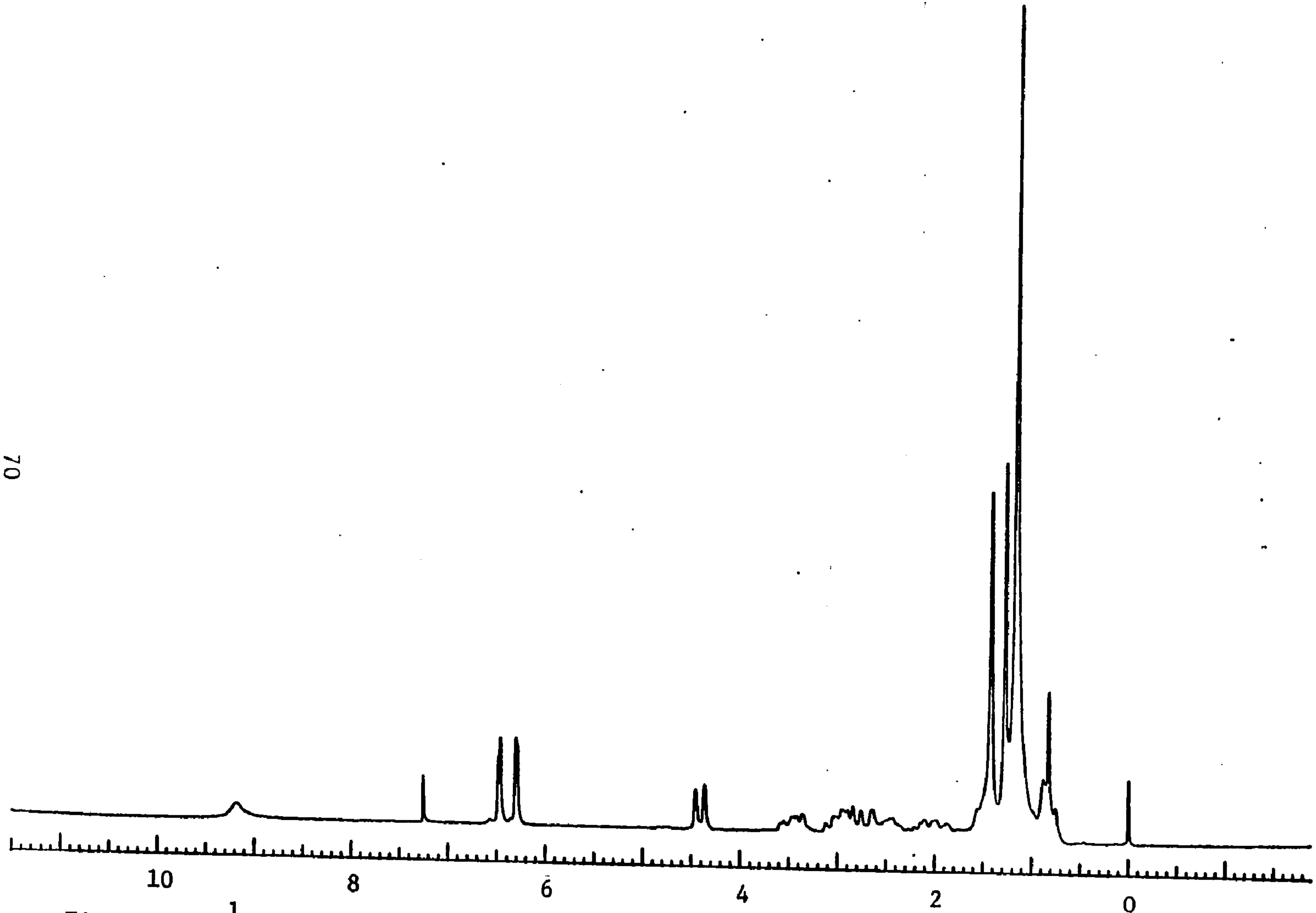


Figure 20: ^{1}HNMR spectrum of 9-Hydroxy-4,4-dimethyl-7-(1,1-dimethylheptyl)-2-3,3,9b-tetrahydrothieno[3,2-c][1]benzopyran-S-oxide.

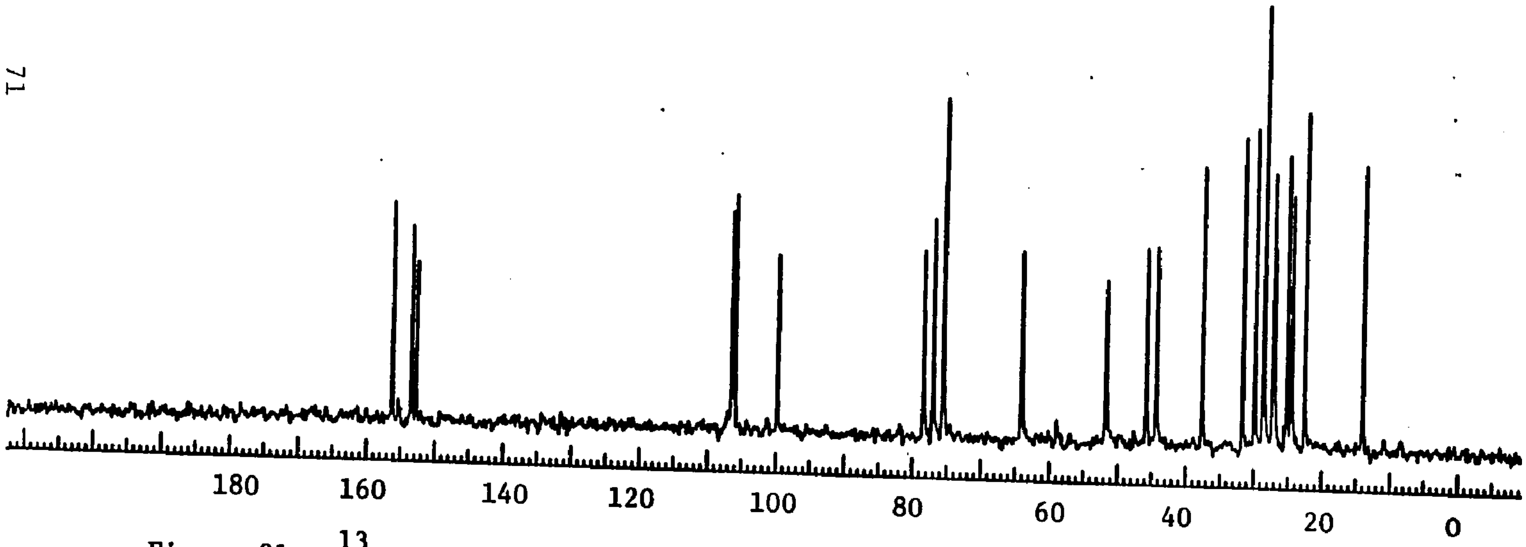


Figure 21: ^{13}CNMR spectrum of 9-Hydroxy-4,4-dimethyl-7-(1,1-dimethylheptyl)-2-3,3,9b-tetrahydrothieno[3,2-c][1]benzopyran-S-oxide.

Sulfoxide(26) - Conformation

Comparison of the minimum energy conformations of (26) and 9-β-hydroxyhexahydrocannabinol (HHC) (Force-field calculations, Allinger's MMI model [27], alkyl side chains abbreviated as methyl groups) demonstrates a gross structural similarity between these molecules (see Figures 22 and 23). Table 6 summarizes data obtained for several compounds presumed to fit the cannabinoid-prostaglandin receptor [26]. While the similarity of the dihedral angles noted for PGE_2 and (26) is encouraging for a good receptor fit, the O-O internuclear distance seen in [26] is significantly lower than the other compounds known to fit this receptor. The fact, however, that 11-hydroxy-THC shows analgetic activity suggests a good degree of flexibility in this portion of the receptor. Biological testing will be untertaken to determine the efficacy of sulfoxide [26] as an analgetic agent.

TABLE 6

Compound	O - O internuclear distance in Å	O-C---CO or O-C---SO dihedral angle
HHC	4.92	50.8°
Levonantradol	4.97	63.6°
PGE_2*	5.11	11.2°
(26)	3.29	15.5°

*x-ray structure data [26]

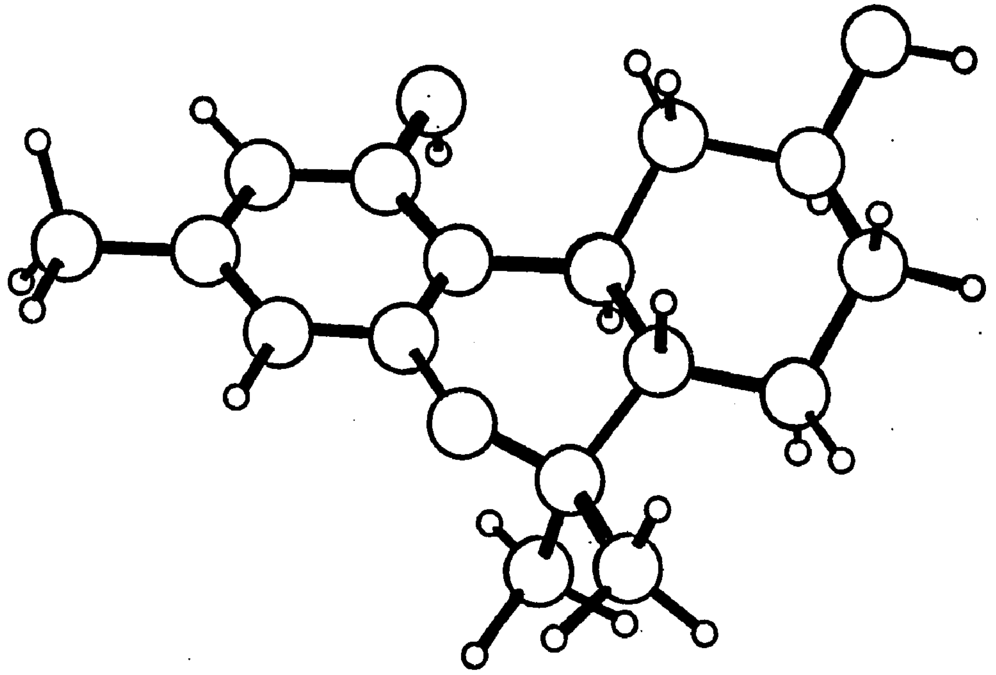


Figure 22: 9-normethyl-9β-hydroxyhexahydrocannabinol (HHC).

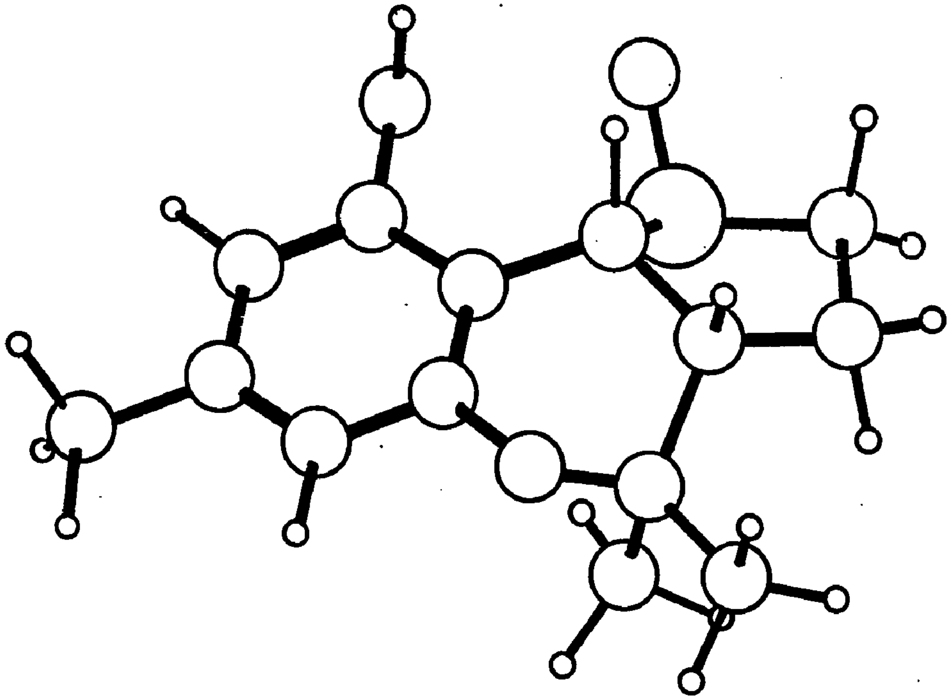


Figure 23: 9-Hydroxy-4,4-dimethyl-7-(1,1-dimethylheptyl)-2-3,3,9b-tetrahydrothieno[3,2-c][1]benzopyran-S-oxide.

EXPERIMENTAL SECTION

General Methods

Solvents and Reagents

Anhydrous solvents were prepared as follows: dimethylformamide was distilled from calcium hydride and stored over 4 Å molecular sieves, benzene was dried over metallic sodium, diethyl ether was dried over "Dri-Na", and methylene chloride was dried over 4 Å molecular sieves. Petroleum ether refers to a hydrocarbon fraction collected from 35° - 60°C. n-Butyl lithium solutions were titrated with diphenylacetic acid [98] prior to use. Aqueous washes were performed using volumes one-quarter to one third that of the organic phase being treated.

Chromatography

Analytical thin layer chromatography (TLC) was performed using Analtech Uniplates silica gel GF (250 µ). Visualization was accomplished through fluorescence and/or spraying with 3% H_2SO_4/MeOH and charring. Preparative TLC was performed on Analtech Uniplates silica gel GF (20 x 20 cm, 500 µ) with loading between 50 and 100 mg/plate. Flash chromatography was performed according to the method of Still [68], utilizing EM 60 silica gel (230-400 mesh). Mesh chromatography was performed according to the method of Taber [92], using "BioSil A" silica gel (100-200 mesh) as absorbant and EM 60 silica gel (230-400 mesh) as column packing.

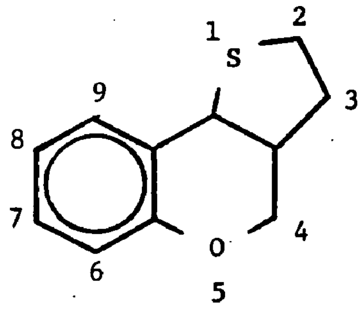
Physical Methods

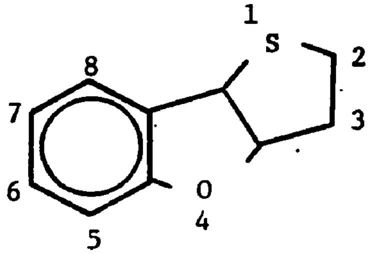
Melting points were determined on a Fisher-Johns melting point apparatus between cover slips or on a Thomas-Hoover melting point apparatus in open capillaries and are reported uncorrected. Elemental analyses were performed by Robertson Laboratories, Inc., Florham Park, NJ. All compounds reported were pure to TLC and/or ^{1}HNMR. Unless otherwise stated, yields are given for analytically pure material.

Spectral Methods

IR spectra were obtained on a Perkin Elmer 238 Spectrometer as nujol mulls, KBr pellets, or in the neat state. Proton NMR spectra were obtained on a JEOL FX90Q spectrometer operating at 89.55 MHz, with TMS as internal standard. ^{1}H NMR data were reported as follows: chemical shift (integral value, multiplicity, coupling constant, assignment). Splitting patterns are designated as follows: s, singlet; d, doublet, t, triplet, q, quartet, qt, quintet; m, multiplet; app, apparent; br, broad. Coupling constants are reported in Hertz (Hz). ^{13}C NMR spectra were obtained on a JEOL FX90Q spectrometer operating at 22.49 MHz. The middle resonance of the deuterated solvent served as internal standard, but all ^{13}C NMR resonances are reported relative to TMS. All ^{13}C NMR spectra obtained were proton-decoupled. Spectral assignments are based on calculation and/or spectral comparison and are therefore tentative.

Spectral assignments are made according to the accepted IUPAC numbering systems, as shown below.





Mass spectra were obtained on a Finnegan Model 4023 spectrometer, with an Incos data system and a solids inlet probe. GC-MS data was obtained on the above instrument using either an SE-30 or an OV-101 column under the following conditions: 100°C for 2 min; increase T 20°C/min to 300°C, hold at 300°C for 5 min, gas flow rate 20 mL/min.

1-Methoxy-3[(tetrahydro-2H-pyran-2-yl)-oxy]benzene(1).

Monomethylresorcinol (12.4g, 0.10 mol), dihydropyran (14 mL, 0.15 mol) and 1.0 g pyridinium tosylate (PPTS) were dissolved in 50 mL dry CH_2Cl_2 and stirred at room temperature for 3 hrs, at which time the reaction mixture was flooded with Et_2O and washed with half-saturated aqueous sodium chloride to remove the catalyst. The organic layer was then washed with 10% aqueous sodium hydroxide (2X), water (1X), and saturated aqueous sodium chloride (2X), and dried over sodium sulfate. Rotary evaporation yielded an oil which was dissolved in dry CH_2Cl_2 (100 mL), which was removed in vacuo to effect the azeotropic removal of residual water. Analytically pure (1) (20.1 g, 96%) remained as a clear oil.

TLC Rf = 0.45 (silica, CH_2Cl_2)

IR (neat, NaCl). 2938, 1591, 1486, 1259, 1194, 1147, 1102, 1072, 1034 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 7.05-7.3 (1H, m, H5), 6.4-6.7 (3H, m, H2,H4,H6), 5.39 (1H, br s, H2´),3.76 (3H, s, OCH_3), 3.4-4.05 (2H, m, H6´) 1.4-2.2 (6H, m, H5, H4´, H5´).

^{13}CNMR ($CDCl_3$) δ 160.65 (C1 or C3), 158.23 (C1 or C3), 129.63 (C5), 108.61 (C4 or C6), 107.15 (C4 or C6), 102.73 (C2), 96.34 (C2´), 61.94 (C6´), 55.14 (OCH_3), 30.30 (C3´), 25.13 (C5´),18.74 (C4´).

Analysis calc. for $C_{12}H_{16}O_3$: C, 69.21; H,7.74

found: C, 68.96; H,7.64.

2-Hydroxy-6-methoxybenzaldehyde(2).

The THP-protected resorcinol (1) (11.45 g, 55 mmol), in 10 mL dry Et_2O, was added dropwise, under N_2, to a mixture of 100 mL dry Et_2O and 60 mmol of n-BuLi in hexanes. Following 1 hr at reflux, the reaction mixture was chilled (icebath) and treated by the dropwise addition of dry DMF (5.4 mL, 70 mmol). After 0.5 hr at room temperature the reaction was quenched by the dropwise addition of cold water. The reaction mixture was then extended with diethylether (150 ml), the organic phase separated and washed with 3N hydrochloric acid (2X), water (1X), and saturated sodium chloride solution (1X). Rotary evaporation of the organic solvents, followed by crystallization of the semi-solid residue from EtOH/H_2O, gave (2) (4.1 g, 49%) as pale yellow crystals, mp 71-72°C (lit.[#55] mp 71.5 - 72.5°C).

IR (nujol) 1640, 1080 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 11.96 (1H, s, OH), 10.33 (1H, s, CHO), 7.41 (1H, app t, J = 8.4 Hz, H4), 6.5 (1H, d, J = 8.4 Hz, H3), 6.37 (1H, d, J = 8.4 Hz, H5), 3.89 (3H, s, OCH_3).

^{13}CNMR ($CDCl_3$) δ 194.29 (CHO), 163.63 (C2 or C6), 162.49 (C2 or C6), 138.35 (C4), 110.86 (C1), 109.86 (C2), 100.95 (C6), 55.79 (OCH_3).

Analysis calc. for $C_8H_8O_3$: C, 63.15; H, 5.30

found: C, 62.97; H, 5.21

Preparation of Tetrahydrothienobenzopyranones(3):

General Procedure.

Equimolar amounts of the appropriate salicylaldehyde and γ-thiobutyrolactone were dissolved in a mixed CH_3CN/DMF solvent system (2:1 or 1:1) to form an ∿ 0.5 molar solution. An equimolar amount of base in the form of 10N aqueous potassium hydroxide was added, and the mixture was refluxed for 6 hrs. Rotary evaporation of the solvents left a golden to red oily residue which was diluted with a 10 volume equivalent of distilled water, chilled in an ice bath, and carefully neutralized by the dropwise addition, with stirring, of 6N hydrochloric acid. The gummy to semi-crystalline residue formed was separated and crystallized from 95% ethanol.

2,3,3a,9b-Tetrahydrothieno[3,2-c][1]benzopyran-4-one.(3a)

Salicylaldehyde (2.50 g, 20.4 mmol) was treated as above to yield 1.54 g (37%) of (3a) as white needles, mp 133-135°C (lit.[52] mp 133-135°C).

IR (KBr) 3065, 2925, 1750, 1610, 1590 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 6.9-7.4 (4H, m ArH) 4.65 (1H, d, J = 5.6 Hz, H9b), 2.85-3.5 (4H, m, H2, H3exo, H3a), 1.9-2.4 (1H, m, H3endo).

^{13}CNMR ($CDCl_3$) δ 167.63 (C4), 150.30 (C5a), 129.39, 128.76, 124.48, 120.99 (C9a), 117.09, 47.20 (C9b), 46.37 (C3a), 32.25 (C2), 30.36 (C3).

Analysis calc. for $C_{11}H_{10}O_2S$: C, 64.06; H, 4.89; S, 15.54

found: C, 63.83; H, 5.11; S, 15.72

8-Chloro-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran-4-one (3b).

5-Chlorosalicylaldehyde (4.7g, 30 mmol) yields (3b) (1.82 g, 25%) as white needles, mp 146-148°C (lit.[52] mp 148-150°C).

IR (KBr) 3100, 2964, 2939, 2903, 1747, 1475, 1416 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 6.9-7.35 (3H, m, ArH), 4.60 (1H, d, J = 5.6 Hz, H9b), 2.8-3.45 (4H, m, H2, H3exo, H3a), 1.95-2.4 (1H, m, H3endo).

^{13}CNMR ($CDCl_3$) δ 166.98 (C4), 148.73 (C5a), 129.47, 129.33, 128.52, 122.75, 118.42, 46.91 (C9b), 45.88 (C3a), 32.25 (C2), 30.33 (C3).

Analysis calc. for $C_{11}H_9ClO_2S$: C, 54.89; H, 3.77; S, 13.32

found: C, 54.97; H, 3.91; S, 13.20

9-Methoxy-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran-4-one (3c).

6-Methoxysalicylaldehyde (3.04 g, 20 mmol) yields 1.73 g (37%) of (3c) as white needles, mp 138-140°C.

IR (KBr) 2980, 2920, 1764, 1610, 1590, 1432, 1245, 1080 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 7.24 (1H, app t, J = 9.3 Hz, $\underline{A}B_2$) 6.6-6.8 (2H, m, $A\underline{B}_2$), 4.93 (1H, d, J = 5.8 Hz, H9b), 3.88 (3H, s, OCH_3), 2.9-3.4 (4H, m, H2, H3exo, H3a), 1.85-2.35 (1H, m, H3endo).

^{13}CNMR ($CDCl_3$) δ 167.69 (C4), 157.29 (C9), 151.22 (C5a), 129.47 (C7), 110.21 (C9a), 109.40 (C6 or C8), 106.28 (C6 or C8), 55.90 (OCH_3), 46.31 (C9b), 40.79 (C3a), 31.93 (C2), 29.98 (C3).

Analysis calc. for $C_{12}H_{12}O_3S$: C, 60.99; H, 5.12; S, 13.57

found: C, 60.85; H, 5.30; S, 13.60

7-Methoxy-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran-4-one (3d).

4-Methoxysalicylaldehyde (1.52 g, 10 mmol) yields 0.30 g (12%) of (3d) as white needles, mp 134-136°C, following recrystallization from EtOH (2x).

IR (KBr) 2970, 2840, 1745, 1622, 1585, 1432, 1235, 1030 cm^{-1}.

^{1}HNMR (CDCl$_3$) δ 7.15 (1H, dd, J = 7.3 Hz, J = 1.4 Hz, H9) 6.65 (1H, dd, J = 7.3 Hz, J = 1.4 Hz, H8), 6.6 (1H, s, H6), 4.63 (1H, d, J = 5.4 Hz, H9b), 3.79 (3H, s, OCH$_3$), 2.8-3.4 (4H, m, H2, H3exo, H3a), 1.95-2.4 (1H, m, H3endo).

^{13}CNMR (CDCl$_3$) δ 167.69 (C4), 160.51 (C7), 151.16 (C5a), 129.33 (C9), 112.84 (C9a), 110.54 (C8), 102.54 (C6), 55.49 (OCH$_3$), 47.37 (C9b), 46.12 (C3a), 32.12 (C2), 30.33 (C3).

Analysis calc. for $C_{12}H_{12}O_3S$: C, 60.99; H, 5.12; S, 13.57
found: C, 61.15, H, 5.23; S, 13.67

Attempted preparation of:
7-Hydroxy-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benozpyran-4-one (3e).

2,4-dihydroxybenzaldehyde (1.38 g, 10 mmol), treated as above, provided a red, resinous film on attempted recrystallization. Efforts to isolate (3c) or 2,4 dihydroxybenzaldehyde by chromatography were unsuccessful.

Attempted preparation of:
9-Hydroxy-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran-4-one (3f).

2,6-dihydroxybenzaldehyde (13) (1.38 g, 10 mmol), treated as above, provided a red, resinous film on attempted recrystallization. Efforts to isolate 2,6-dihydroxybenzaldehyde (13) or (3f) by chromatography were unsuccessful.

Preparation of Tetrahydrothieno-diols (4): General Procedure.

The appropriate tetrahydrothienobenzopyranone (3) (1eq.), dissolved in a minimum of dry benzene, was added dropwise to a 1 molar solution of CH_3MgI (4 eq) in dry ether. The reaction mixture was stirred at room temperature for 18 hrs, refluxed for 2 hrs, and quenched by the dropwise addition of saturated aqueous ammonium chloride (ice bath). The organic phase was separated, the aqueous phase extracted with benzene (2X), and the combined organic phases dried over sodium sulfate. Rotary evaporation to a miminum volume led to the deposition of compounds (4) as analytically pure crystals.

2-(2-Hydroxyphenyl)-3-(1-hydroxy-1-methylethyl)tetrahydrothiophene (4a).

Tetrahydrothienocoumarin (3a), (7.90 g, 38.4 mmol), treated as above, yielded 7.90 g (86%) of (4a) as a white crystalline solid, mp 192-194°C.

IR (KBr) 3327, 2970, 2937, 1602, 1589, 1232, 1159 cm^{-1}.

^{1}HNMR (DMSO-d6) δ 9.62 (1H, br s, ArOH), 6.65-7.5 (4H, m, ArH), 4.83 (1H, d, J = 5.9 Hz, H2), 1.75-3.4 (6H, m, H3, H4, H5, ROH), 0.86 (3H, s, CH_3), 0.80 (3H, s, CH_3).

^{13}CNMR (DMSO-d6) δ 153.35 (C2′), 131.79, 130.57, 127.48, 119.30 (C5′), 115.70 (C3′), 71.08 (COH), 61.55 (C2), 42.75 (C3), 29.21 (C5), 28.75 (C4), 28.53 (CH_3), 26.77 (CH_3).

Analysis calc. for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61; S, 13.45

found: C, 65.81; H, 7.58; S, 13.52

2-(5-Chloro-2-hydroxyphenyl)-3-(1-hydroxy-1-methylethyl)tetrahydrothiophene (4b).

Chlorothienocoumarin (3b) (1.2 g, 5.0 mmol) yields 1.20 g (87%) of (4b) as a white crystalline solid, mp 190-192°C.

IR (KBr) 3358, 2967, 1596, 1458, 1263, 1231, 1052, 1021 cm^{-1}.

^{1}HNMR (DMSO-d6) δ 7.3 (1H, br s, ArOH), 7.35 (1H, d, J = 2.5 Hz, H6´), 7.05 (1H, dd, J = 8.5 Hz, J = 2.5 Hz, H4´), 6.75 (1H, d, J = 8.5 Hz, H3´), 4.77 (1H, d, J = 6.1 Hz, H2), 1.8-2.65 (6H, m, H3, H4, H5, ROH), 0.88 (3H, s, CH_3), 0.85 (3H, s, CH_3).

^{13}CNMR (DMSO-d6) δ 152.51 (C2´), 133.06, 131.16, 127.15, 122.60 (C5´), 117.30 (C3´), 70.81 (COH), 61.28 (C2), 42.59 (C3), 29.21 (C5), 28.67 (C4), 27.42 (CH_3's).

Analysis calc. for $C_{13}H_{17}ClO_2S$: C, 57.24; H, 6.28; S, 11.75

found: C, 57.22; H, 6.33; S, 11.74

2-(6-Methoxy-2-hydroxyphenyl)-3-(1-hydroxy-1-methylethyl)tetrahydrothiophene (4c).

Methoxythienocoumarin (3c), (1.18 g, 5.0 mmol), yields 1.14 g (84%) of (4c) as white crystals, mp 171-173°C.

IR (KBr) 3432, 3147, 2963, 2942, 2863, 1591, 1496, 1249, 1081 cm^{-1}.

^{1}HNMR (DMSO-d6) δ 9.5/9.44 (1H, pr. of s, rotamers, ArOH), 7.05 (1H, app t, J = 8.0 Hz, H4´), 6.40 (2H, app d, J = 8.0 Hz, H3´, H5´), 5.12 (1H, app t (pr. of doublets-rotamers), J = 6.2 Hz, H2), 4.20/4.09 (1H, pr. of s, rotamers, ROH), 3.71 (3H, s, OCH_3) 2.1-3.4 (5H, m, H3, H4, H5), 0.96 (3H, s, CH_3) 0.80 (3H, s, CH_3).

^{13}CNMR (DMSO-d6) δ 159.12 (C6′), 154.68 (C2′), 128.24 (C4′), 118.16 (C1′), 108.52 (C3′ or C5′), 103.47 (C3′ or C5′), 70.87 (COH), 61.87 (C2), 55.16 (OCH_3), 41.30 (C3), 31.16 (C5), 30.62 (C4), 28.56 (CH_3), 26.40 (CH_3).

Analysis calc. for $C_{14}H_{20}O_3S$: C, 62.65; H, 7.51; S, 11.95

found: C, 62.75; H, 7.36; S, 11.90.

2-(4-Methoxy-2-hydroxyphenyl)-3-(1-hydroxy-1-methylethyl)tetrahydrothiophene (4d).

Methoxythienocoumarin (3d), (1.18 g 5.0 mmol), yields 1.11 g (83%) of (4d) as white crystals, mp 155-156°C.

IR (KBr) 3360, 2970, 2845, 1608, 1511, 1228, 1030 cm^{-1}.

^{1}HNMR (DMSO-d6) δ 9.67 (1H, br s, ArOH), 7.28 (1H, d, J = 8.4 Hz, H6′), 6.40 (1H, dxd, J = 8.4 Hz, J = 2.9 Hz, H5′), 6.32 (1H, d, J = 2.9 Hz, H3′), 4.8 (1H, s, ROH), 4.74 (1H, d, J = 5.9 Hz, H2), 3.67 (3H, s, OCH_3), 1.8-3.2 (5H, m, H3, H4, H5), 0.87 (3H, s, CH_3), 0.81 (3H, s, CH_3).

^{13}CNMR (DMSO-d6) δ 158.68 (C4), 154.18 (C2), 132.41 (C6′), 122.66 (C1′), 105.38 (C3′ or C5′), 101.04 (C3′ or C5′), 71.08 (COH), 61.28 (C2), 54.78 (OCH_3), 42.53 (C3), 29.10 (C5), 28.78 (C4), 28.50 (CH_3), 26.82 (CH_3).

Analysis calc. for $C_{14}H_{20}O_3S$: C, 62.65; H, 7.51; S, 11.95

found: C, 62.47; H, 7.61; S, 12.00.

Cyclization of Diol (4a): Preparation of *cis + trans* 4,4-dimethyl-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran (5).

Method (A)

Diol (4a), (0.50 g, 2.1 mmol) was suspended in 20 mL dry CH_2Cl_2 to which 0.1 g p-TSA had been added. Following a 2 hr reflux, the reaction mixture was diluted with ether, washed successively with saturated aqueous sodium bicarbonate (2X), water (1X), and saturated aqueous sodium chloride (1X), and dried over sodium sulfate. Flash chromatography (CH_2Cl_2) led to the isolation of (5) (0.4 g, 86%) as green oil identical in all respects to the material prepared by method (B).

Method (B)

Diol (4a) (1.00 g, 4.2 mmol) was dissolved in 10 mL TFA and stirred at room temperature for 2 hrs. Rotary evaporation of the solvent left a red oil which was purified by flash chromatography (CH_2Cl_2) to yield the title compounds (0.92 g, 99%) as an intimate mixture of isomers (7.3, *cis/trans* by integration of ^{1}HNMR H9b resonances).

TLC Rf = 0.85 (silica, CH_2Cl_2).

IR (KBr) 3052, 2951, 1601, 1574, 1245, 1060, 1030 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 6.4-7.3 (4H, m, ArH), 4.51 (0.7H, d, J = 6.6 Hz, H9b*cis*), 4.22 (0.3H, d, J = 10.5 Hz, H9b*trans*), 2.8-3.25 (2H, m, H2), 1.55-2.45 (3H, m, H3, H3a), 1.43 (0.9H, s, CH_3*trans*), 1.40

(2.1H, s, CH_3*cis*), 1.25 (2.1H, s, CH_3*cis*), 1.20 (0.9H, s, CH_3 *trans*).

^{13}CNMR 152.76 (*cis* C5a), 150.95 (*trans* C5a), 130.58 (*cis* + *trans* C7), 128.19 , 127.65, 124.48 (*cis* C9a), 123.32 (*trans* C9a), 120.75, 119.64, 78.54 (*trans* C4), 74.91 (*cis* C4), 55.76 (*trans* C9b), 51.86 (*cis* C9b), 44.88, 43.77, 30.84, 30.60, 29.84, 29.63, 29.33, 28.19, 25.91, 20.77.

MS (*cis*) m/z (%) $M^{+\cdot}$ 220 (100), 205 (54.4), 177 (11.4), 171 (2.9), 159 (6.2), 158 (2.4), 145 (9.7), 137 (12.6), 115 (9.4), 91 (3.5), 77 (2.3), 59 (1).

(*trans*) m/z (%)($M^{+\cdot}$ 220 (100), 205 (10.6), 177 (14.3), 171 (7.7), 159 (10.6), 145 (11.1), 137 (30.9), 115 (12.4), 107 (4.9), 59 (< 1).

Analysis calc. for $C_{13}H_{16}OS$: C, 70.86; H, 7.32; S, 14.55

found: C, 70.61; H, 7.36; S, 14.35

Cyclization of Diol (4b): Preparation of *cis* + *trans* 8-Chloro-4,4-dimethyl-2,3,3a,9b-tetrahydrothieno-[3,2-c][1]benzopyran (6).

Diol (4b), (0.72 g, 2.7 mmol) was dissolved in 10 mL TFA and stirred at room temperature for 2 hrs. Rotary evaporation, followed by flash chromatography (CH_2Cl_2) of the resultant red oil gave pyrans (6), (0.64 g, 94%), as a green oil that solidified on standing, mp 72-74°C. (*cis/trans* ratio = 4:1 by ^{1}HNMR, integration of H9b resonances).

TLC Rf = 0.76 (silica, CH_2Cl_2).

IR (KBr) 2974, 2862, 1601, 1568, 1472, 1286, 1253, 1083, 1062 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 6.6-7.3 (3H, m, ArH), 4.47 (0.8H, d, J = 6.4 Hz, H9b *cis*), 4.19 (0.2H, d, J = 11.4 Hz, H9b *trans*), 2.9-3.25 (2H, m, H2), 1.6-2.5 (3H, m, H3, H3a), 1.56 (3H, br s, CH_3 *cis* + *trans*), 1.45 (2.4H, s, CH_3 *cis*), 1.31 (0.6H, s, CH_3 *trans*).

^{13}CNMR ($CDCl_3$) *cis* compd. δ 149.56 (C5a), 130.09, 127.63, 126.02, 125.11, 118.12, 75.29 (C4), 51.43 (C9b), 43.41 (C3a), 30.49 (C2), 29.43 (C3), 27.95 (CH_3), 25.75 (CH_3).

trans compd. δ 151.38 (C5a), 130.09, 127.98, 125.01, 124.05, 117.44, 78.95 (C4), 55.44 (C9b), 44.36 (C3a), 30.95 (CH_3), 29.76 (C2), 29.09 (C3), 20.66 (CH_3).

MS *(cis)* m/z (%) M + 2, 256 (37), $M^{+\cdot}$ 254 (100), 241 (35), 239 (95.6), 219 (11.1), 213 (11.1), 211 (30.3), 195 (6.5), 193 (13.6), 181

(7.3), 179 (22.3), 115 (21.2), 77 (6.9), 59 (4.8).
(*trans*)m/z (%) M + 2, 256 (35.6), $M^{+\cdot}$ 254 (92.5), 241 (36.7), 239 (100), 219 (7.4), 213 (11.9), 211 (21.5), 195 (5.7), 193 (15.3), 181 (5.1), 179 (13.0), 115 (16.7), 77 (8.8), 69 (3.8), 55 (10.2).

Analysis calc. for $C_{13}H_{15}Cl\ O\ S$: C, 61.28; H, 5.93; S, 12.59
found: C, 61.05; H, 5.86; S, 12.78.

Cyclization of Diol (4c)

Method (A).

0.50 g (1.9 mmol) of diol (4c) was dissolved in 5 mL TFA and stirred for 2 hrs. Rotary evaporation to a red oil was followed by flash chromatography (CH_2Cl_2, fractions more migratory than starting material collected) to yield 0.27 g (58%) of a green oil. Half of this material was purified by prep TLC (2:1 pet. ether/ CH_2Cl_2, 3 elutions) and checked by ^{1}HNMR spectroscopy, which revealed a mixture of isomeric material, identical to the crude material described below.

Method (B).

0.45 g (1.7 mmol) of diol (4c) was suspended in 40 mL dry CH_2Cl_2 containing a catalytic amount of p-TSA and refluxed for 8 hrs. The reaction mixture was extended with ether and washed successively with saturated aqueous sodium bicarbonate (2X), water (1X), and saturated aqueous sodium chloride. The organic phase was dried overnight (Na_2SO_4). Flash chromatography (CH_2Cl_2, fractions more migratory than starting material collected) gave a green oil (0.34 g, 80%) which was further purified by successive applications of flash chromatography (2:1 CH_2Cl_2/pet. ether followed by 3:4 CH_2Cl_2/pet. ether) to yield the following products:

<u>2-(2-Hyroxy-6-methoxyphenyl)-3-(1-methylethylidene)tetrahydrothiophene (7).</u>

TLC Rf = 0.48 (silica, 2:1 CH_2Cl_2/pet. ether, 18.5%) golden oil.
IR (KBr) 3511, 3432, 2960, 2837, 1661, 1607, 1585, 1467, 1439, 1364, 1262, 1220, 1085 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 7.0-7.2 (1H, t, J = 7.6 Hz, H4´), 6.35-6.65 (2H, m, H3´, H5´), 6.02 (1H, br s, H2), 4.55 (1H, br s, OH), 3.77 (3H, s, OCH_3), 2.6-3.0 (4H, m, H4, H5), 1.64 (6H, s, CH_3).

^{13}CNMR ($CDCl_3$) δ 157.75 (C6´), 156.39 (C2´), 153.12 (C3), 128.66 (C4´), 113.05 (C9a), 109.72 (C3´ or C5´), 107.93 (C3´ or C5´), 102.62 (C1´), 55.66 ($O\underline{C}H_3$), 53.98 (C2), 34.07 (C5), 31.25 (C4), 27.89 (CH_3).

MS m/z (%) $M^{+\cdot}$ 250 (42.1), 235 (100), 207 (9.6), 203 (4.2), 189 (17.4), 175 (7.0), 167 (3.8), 137 (9.3), 115 (11.2), 107 (4.7), 91 (5.3), 79 (5.4), 77 (8.7), 69 (2.8).

Analysis calc. for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25; S, 12.81
found: C, 67.11; H, 7.36; S, 12.79.

<u>8-Methoxy-3a-(1-methoxy-3a-(1-methylethyl)-2,3,3a,8b-tetrahydrothieno[3,2-b]benzofuran (8).</u>

TLC Rf = 0.55 (silica, 3:4 CH_2Cl_2/pet. ether, 9.7%) golden oil.

IR (KBr) 2963, 2936, 1600, 1490, 1456, 1289, 1259, 1229, 1087 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 7.1 (1H, m app. t, J = 8.4Hz, H6), 6.45 (2H, m, H5, H7), 4.72 (1H, s, H8b), 3.85 (3H, s, OCH_3), 1.85-3.05 (4H, m, H2, H3), 2.15 (1H, q, J = 6.6Hz, H1´),1.05 (3H, d, J = 6.6Hz, CH_3), 0.98 (3H, d, J = 6.6Hz, CH_3)

^{13}CNMR ($CDCl_3$) δ 160.43 (C4a or C8), 155.93 (C4a or C8), 129.98 (C6), 117.47 (C8a), 103.00 (C5 or C7), 102.14 (C5 or C7), 55.49 (OCH_3), 52.62 (C3a), 41.19 (C8b), 35.56 (C2), 31.06 (C3), 25.70 (C1´), 17.95 ($\underline{C}H_3$), 17.79 ($\underline{C}H_3$).

MS (*cis*) m/z (%) $M^{+\cdot}$250 (60.8), 235 (100), 207 (17.8), 189 (10.7), 175 (18.1), 167 (7.8), 137 (4.7), 115 (5.9), 91 (6.7), 79 (3.1), 77 (5.3).

Analysis calc. for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25; S, 12.81
found: C, 67.39; H, 7.24; S, 12.60.

cis + trans 9-Methoxy-4,4-dimethyl-2,3,3a,9b-tetrahydrothieno-[3,2-c][1]benzopyran (9).

TLC Rf = 0.40 (silica, 3:4 CH_2Cl_2/pet. ether, 72%) green oil, *cis : trans* ratio 4:1, integration of ^{1}HNMR H9b resonances.

IR (KBr) 3068, 2971, 2934, 2861, 2836, 1605, 1589, 1464, 1439, 1251, 1217, 1085 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 7.05 (1H, app t, J = 8.5Hz, H7), 6.4 (2H, m, H6, H8), 4.53 (0.8H, d, J = 7.6Hz, H9b*cis*), 4.10 (0.2H, d, J = 10.7Hz, H9b*trans*), 3.84 (3H, s, OCH_3), 2.7-3.1 (2H, m, H2), 1.6-2.4 (3H, m, H3, H3a), 1.45 (3H, s, CH_3 *cis + trans*), 1.25 (2.4H, s, CH_3*cis*), 1.18 (0.6H, s, CH_3 *trans*).

^{13}CNMR ($CDCl_3$) δ 161.78, 158.10, 128.84, 128.19, 127.65, 114.30, 109.75, 109.50, 102.76, 101.95, 77.87(*trans* C4), 75.10 (*cis* C4), 55.47, 55.36, 55.30, 50.48, 41.46, 39.95, 31.17, 30.14, 29.54, 28.81, 28.03, 25.02, 19.60.

MS (*cis*) m/z (%) $M^{+\cdot}$250 (60.8), 235 (100), 207 (17.8), 203 (8.6), 189 (6.8), 175 (11.0), 167 (16.8), 137 (4.8), 115 (6.4), 103 (4.0), 91 (4.5), 77 (6.6), 59 (2.7).
(*trans*) m/z (%) $M^{+\cdot}$250 (63.8), 235 (100), 207 (32.7), 203 (9.5), 189 (8.2), 175 (10.0), 167 (26.8), 137 (5.6), 115 (9.5), 107 (6.6), 103 (4.8), 91 (6.6), 77 (5.2), 55 (7.4).

Analysis calc. for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25; S, 12.81
found: C, 66.87; H, 7.18; S, 12.95.

Cyclization of Diol (4d): Preparation of *cis* + *trans* 7-Methoxy-4,4-dimethyl-2,3,3a,9b-tetrahydrothieno[3,2-c][1]-benzopyran (10).

Diol (4d), (0.70 g, 2.6 mmol), was suspended in 40 mL dry CH_2Cl_2 containing a catalytic amount of p-TSA and refluxed for 8 hrs. The reaction mixture was extended with CH_2Cl_2, washed successively with saturated aqueous sodium bicarbonate (2X), water (1X), and saturated aqueous sodium chloride (1X), and dried over sodium sulfate. Flash chromatography (CH_2Cl_2, collect all fractions more migratory than the starting material) gave 0.55 g (85%) of a golden oil that was further purified (flash chromatography, 5:1 CH_2Cl_2/pet. ether) to yield the resinous title compounds (0.37 g, 51% from starting material) as an intimate mixture (4:1, *cis/trans*, by integration of the ^{1}HNMR H9b resonances).

TLC Rf = 0.51 (silica, 5:1 CH_2Cl_2/pet. ether).

IR (neat, NaCl) 2930, 2810, 1605, 1540, 1490, 1432, 1273, 1255, 1085, 1035 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 6.85 - 7.25 (1H, m, H9), 6.3-6.6 (2H, m, H6, H8), 4.49 (0.8H, d, J = 6.3Hz, H9b *cis*), 4.18 (0.2H, d, J = 11.2Hz, H9b *trans*), 3.73 (3H, s, OCH_3), 2.7-3.2 (2H, m, H2), 1.55-2.5 (3H, m, H3, H3a), 1.47 (0.6H, s, CH_3 *trans*), 1.44 (2.4H, s, CH_3 *cis*), 1.32 (2.4H, s, CH_3 *cis*), 1.24 (0.6H, s,

CH_3 *trans).*

^{13}CNMR ($CDCl_3$) *cis* δ 159.35 (C7), 151.81 (C5a), 131.26 (C9), 116.71 (C9a), 108.23 (C8), 101.11 (C6), 75.27 (C4), 55.09 (OCH_3), 51.97 (C9b), 43.49 (C3a), 30.63 (C2), 29.60 (C3), 28.19 ($\underline{C}H_3$), 25.99 (CH_3)

trans 159.86 (C7), 153.66 (C5a), 128.76 (C9), 115.68 (C9a), 106.50 (C8), 101.11 (C6), 78.79 (C4), 56.14 (C9b), 55.09 ($O\underline{C}H_3$), 44.47 (C3a), 30.87 (C2), 29.74 (C3), 29.30 ($\underline{C}H_3$) , 20.63 ($\underline{C}H_3$).

MS (*cis)* m/z (%) $M^{+\bullet}$250 (29.8), 235 (100), 207 (7), 203 (14.2), 189 (12.5), 175 (27.2), 167 (45.9), 137 (7.6), 115 (28.4), 103 (20.9), 91 (24.9), 79 (18.5), 78 (16.3), 77 (49.6), 69 (40), 61 (7.6) 59 (23.8).

(trans) m/z (%) $M^{+\bullet}$250 (33.3), 235 (100), 207 (9.7), 203 (15.6), 189 (14.6), 175 (25.1), 167 (70.6), 137 (34.6), 115 (31.9), 103 (20), 91 (27.7), 79 (19.1), 78 (16.6), 77 (52.3), 69 (47.9), 61 (8.6), 59 (25.5).

Analysis calc. for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25; S, 12.81
found: C, 66.96; H, 7.21; S, 12.82.

Preparation of Dimethylthienobenzopyrans (11):

General Procedure

The appropriate *cis* and *trans* mixture of thienobenzopyrans (1 eq), was dissolved in dry benzene (5-10 mL/mmol) and treated by the addition of dichlorodicyanoquinone(DDQ) (2.1eq). Refluxing was initiated and continued until TLC indicated complete consumption of the starting material. The reaction mixture was then extended with ether, washed with 10% aq NaOH (2X) followed by saturated aq. NaCl (2X), and dried over Na_2SO_4. The title compounds were then purified by flash chromatography.

4,4-Dimethyl-thieno[3,2-c][1]benzopyran (11a).

The tetrahydrothienobenzopyrans (5) (0.55 g 2.5 mmol) gave, following 3 days at reflux,0.48 g (89%) of (11a) as a red oil after flash chromatography (2:1 pet. ether/CH_2Cl_2).

TLC Rf = 0.60 (silica, 2:1pet. ether/CH_2Cl_2).

IR (neat, NaCl) 3100, 3070, 2970, 2920, 2860, 1600, 1550, 1480, 1242, 1050 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 6.65-7.35 (6H, m, ArH), 1.55 (6H, s, CH_3)

^{13}CNMR ($CDCl_3$) δ 151.08 (C5a), 139.76, 130.98, 128.55, 124.05, 123.73, 122.21, 119.72, 117.04, 78.25 (C4), 28.16 ($\underline{C}H_3$)

Analysis calc. for $C_{13}H_{12}O$ S: C, 72.18; H, 5.59; S, 14.82

found: C, 72.19; H, 5.32; S, 14.55.

8-Chloro-4.4-dimethyl-thieno[3,2-c][1]benzopyran (11b).

The tetrahydrothienobenzopyrans (6), 0.54 g (2.1 mmol), refluxed for 3 days, gave 0.52 g (96%) of (11b) as a green oil following flash chromatography (2:1 pet. ether/CH_2Cl_2)

TLC Rf = 0.75 (silica, 2:1 pet. ether/CH_2Cl_2).

IR (neat, NaCl) 3095, 3060, 2962, 2920, 1595, 1475, 1238, 1080 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 7.13 (1H, d, J = 2.5 Hz, H9), 7.04 (1H, d, J = 5.5 Hz, H2), 6.94 (1H, dd, J = 8.5 Hz, J = 2.5 Hz, H7), 6.71 (1H, d, J = 8.5 Hz, H6), 6.70 (1H, d, J = 5.5 Hz H3), 1.49 (6H, s, CH_3).

^{13}CNMR ($CDCL_3$) δ 151.33 (C5a), 140.57, 129.82, 128.14, 126.03, 125.11, 123.89, 122.32, 121.18, 118.39, 78.79 (C4), 28.19 (CH_3).

Analysis calc. for $C_{13}H_{11}O\ S\ Cl$: C, 62.26; H,4.42; S, 12.79
found: C, 62.52; H,4.42; S, 12.87.

9-Methoxy-4,4-dimethyl-thieno[3,2-c][1]benzopyran. (11c)

The tetrahydrotheinobenzopyrans (9), 68 mg (0.27 mmol), refluxed for 24 hrs, gave (11c) as as a white solid, mp 95-97°C (45 mg, 68%) following flash chromatography (2:1 pet. ether/CH_2Cl_2).

TLC Rf = 0.43 (silica, 2:1 pet. ether/CH_2Cl_2).

IR (KBr) 3092, 2960, 2834, 1582, 1464, 1438, 1278, 1249, 1084 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 7.24 (1H, d, J = 5.2 Hz, H2), 7.08 (1H, t, J = 8.3 Hz, H7), 6.85 (1H, d, J = 5.2 Hz, H3), 6.64 (1H, dd, J = 8.3 Hz, J = 1.0 Hz, H6), 6.57 (1H, dd, J = 8.3 Hz, J = 1.0 Hz, H8), 396 (3H, s, OCH_3), 1.62 (6H, s, CH_3).

^{13}CNMR ($CDCl_3$) δ 154.25 (C9), 152.14 (C5a), 138.60, 127.87, 126.68, 125.32, 122.29, 110.10, 109.83, 103.55, 78.19 (C4), 55.71 (OCH_3), 28.25 (CH_3).

Analysis calc. for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73; S, 13.02

found: C, 67.99; H, 6.03; S, 12.86.

7-Methoxy-4,4-dimethyl-thieno[3,2-c][1]benzopyran (11d).

The isomeric tetrahydrothienobenzopyrans (10), (260 mg, 1.04 mmol), refluxed for 24 hrs, yielded (11d) (202 mg, 79%) as a green oil following flash chromatography (2:1 CH_2Cl_2/pet. ether).

TLC Rf = 0.55 (2:1 CH_2Cl_2/ pet. ether).

IR (neat, NaCl) 3102, 2978, 2836, 1616, 1582, 1462, 1437, 1285, 1273, 1083 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 7.2 (1H, dd, J = 8.6 Hz, J = 1.0 Hz, H9), 7.08 (1H, d, J = 5.1 Hz, H2), 6.79 (1H, d, J = 5.1 Hz, H3), 6.52 (1H, d, J = 1.0 Hz, H6), 6.43 (1H, dd, J = 8.6 Hz, J = 2.5 Hz, H8), 3.76 (3H, s, OCH_3), 1.60 (6H, s, CH_3).

^{13}CNMR ($CDCl_3$) δ 160.37 (C7), 152.41 (C5a), 137.84, 131.23, 123.64, 123.37, 122.67, 113.13, 107.46, 102.62, 78.68 (C4), 55.22 (OCH_3), 28.19 (CH_3).

Analysis calc. for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73; S, 13.02

found: C, 68.27; H, 5.83; S, 13.20.

2,6-Dimethoxybenzaldehyde (12).

Dimethylresorcinol (7.60 g, 55 mmol) in 10 ml dry ether was added dropwise, under nitrogen, to a 3-neck round bottom containing 100 mL dry ether and 60 mmol of an n-butyl lithium solution in hexanes. After the addition was complete, the solution was refluxed for 1 hr, with the white phenyl lithium salt precipitating as the reaction proceeded. The reaction mixture was then chilled (icebath) and treated by the addition, with stirring, of dry DMF (5.4 mL, 70 mmol). After 0.5 hr at room temperature, the reaction was quenched by the dropwise addition of cold water (exothermic). The organic phase was then separated, the aqueous phase twice extracted with ethyl acetate and the combined organic phases washed successively with saturated aqueous ammonium chloride (2X), water (2X), and saturated aqueous sodium chloride (2X), then dried over sodium sulfate. Rotary evaporation yielded a semi-crystalline residue which was crystallized from ether/pet. ether to provide (12) (4.98 g,55%) as white crystals, mp 97-98°C (lit.56; 98-99°C).

IR (KBr) 1680 cm^{-1}).

^{1}HNMR ($CDCl_3$) δ 10.52 (1H, s, CHO), 7.46 (1H, split t, J_{app} = 8.5 Hz, $\underline{A}B_2$), 6.59 (2H, d, J_{app} = 8.5 Hz, $A\underline{B}_2$), 3.90 (6H, s, OCH_3).

^{13}CNMR ($CDCl_3$) δ 189.17 (CHO), 162.00 (C2, C6), 135.78 (C4), 114.14 (C1), 103.71 (C3, C5), 55.87 (OCH_3).

Analysis calc. for $C_9H_8O_3$: C, 65.05; H, 6.07

found: C, 65.26; H, 6.16.

2,6-Dihydroxybenzaldehyde (13).

2,6-dimethoxybenzaldehyde (4.60 g, 27.6 mmol) was treated with aluminum bromide in carbon disulfide according to the method of Adams and Bockstahler to yield (13) (2.55 g, 67%) as pale yellow crystals from water, mp 155-156°C (lit. 155-156°C).

IR (KBr) 3265, 1640 cm^{-1}.

^{1}HNMR (DMSO-d6) δ 11.25 (2H, s, OH), 10.24 (1H, s, CHO), 7.35 (1H, split t, J = 8.5 Hz, $\underline{A}B_2$), 6.36 (2H, d, J = 8.5 Hz, $A\underline{B}_2$).

^{13}CNMR (DMSO-d6) δ 194.28 (CHO), 162.00 (C2, C6), 138.91 (C4), 109.98 (C1), 106.62 (C3, C5).

Analysis calc. for $C_7H_6O_3$: C, 60.87; H, 4.38
found: C, 60.83; H, 4.29.

2-Hydroxy-6-[(tetrahydro-2H-pyran-2-yl)-oxy]benzaldehyde (14).

To a refluxing suspension of 2,6-dihydroxybenzaldehyde (3.00 g, 21.7 mmol) in 150 mL dry CH_2Cl_2 was added PPTS (0.55 g, 2.2 mmol) and dihydropyran (2.0 mL, 22 mmol). After 1 hr the solvent volume was reduced to ∿ 30 mL (rotary evaporation), the dihydropyran replenished (1.5 mL), and the reaction mixture brought to reflux. Approximately 3 hrs later the reaction mixture was diluted with 150 mL ether, washed with half-saturated aqueous sodium chloride (2X) to remove the catalyst, and dried over sodium sulfate. Purification by flash chromatography (2:1 pet. ether/ether) gave 3.94 g (82%) of (14) as a pale green oil.

TLC Rf = 0.54 (silica, 2:1 pet. ether/ether).

IR (neat, NaCl plates) 3200 (br), 2938, 2870, 1645, 1620, 1030 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 11.86 (1H, s, OH), 10.42 (1H, s, CHO), 7.39 (1H, t, J = 8.5 Hz, H4), 6.59 (2H, app t,, J = 8.5 Hz, H3, H5), 5.55 (1H, br. s, H2´), 3.5-4.0 2H, m, H6´), 1.50-2.0 (6H, m, H3´, H4´, H5´)

^{13}CNMR ($CDCl_3$) δ 194.29 (CHO), 163.27 (C2), 159.86 (C6), 138.38 (C4), 111.32 (C1), 110.29 (C3), 104.60 (C5), 96.50 (C2´), 62.13 (C6´), 29.98 (C3´), 24.91 (C5´), 18.46 (C4´).

MS, m/z (rel intens) $M^{+\cdot}$222 (44), 139 (100), 138 (35), 137 (55), 108 (9), 83 (11), 81 (27), 58 (6), 57 (60), 56 (11), 55 (39).

Analysis calc. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35
found: C, 63.54; H, 6.17.

9-[(Tetrahydro-2H-pyran-2-yl)-oxy]-2,3,3a,9b-tetrahydrothieno-[3,2-c][1]benzopyran-4-one (15).

3.70g (16.7 mmol) of the mono-protected dihydroxybenzaldehyde (14), treated according to the general procedure for compound (3), yields 1.60 g (31%) of (15) as a white powder, mp 127-128°C.

IR (KBr) 2928, 2875, 1750, 1608, 1592, 1462, 1040, 1030, 1020 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 6.5-7.35 (3H, m, ArH), 5.59 (1H, br s, H2´), 4.99 (1H, d, J = 6.1 Hz, H9b), 2.85-4.05 (6H, m, H2, H3exo, H3a, H6´), 1.4-2.4 (7H, m, H3endo, H3´, H4´, H5´).

^{13}CNMR ($CDCl_3$) δ 168.12 (C4), 154.23 (C9), 150.95 (C5a), 129.30 (C7), 110.75 (C9a), 109.61 (C6 or C8), 109.56 (C6 or C8), 95.28 (C2´), 61.45 (C6´), 46.10 (C9b), 40.89 (C3a), 32.20 (C2), 30.06 (C3), 29.98 (C3´), 25.07 (C5´), 17.95 (C4´).

Analysis calc. for $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92; S, 10.47

found: C, 62.45; H, 5.95; S, 10.73.

9-Hydroxy-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran-4-one (16).

THP protected thienolactone (15) (612 mg, 2.0 mmol) was dissolved in 20 mL 95% EtOH, to which was added 50 mg (0.2 mmol) PPTS. Stirring at 55°C was continued until (15) was consumed as indicated by the loss of TLC spot (silica, CH_2Cl_2, Rf = 0.40). Purification by mesh chromatography (2 g silica absorbant,100-200 mesh, 2:1 ether/pet. ether) gave 0.39 g (89%) of (16) as a white crystalline solid, mp 185-187°C.

TLC Rf = 0.52 (silica, 2:1 ether/pet. ether).

IR (KBr) 3410, 2925, 1726, 1610, 1595, 1458, 1430, 1248, 1025 cm^{-1}.

^{1}HNMR (DMSO-d6) δ 10.17 (1H, S, OH), 7.13 (1H, t, J = 7.9 Hz, H7), 6.63 (1H, dd, J = 7.9 Hz, J = 0.9 Hz, H6 or H8), 6.52 (1H, dd, J = 7.9 Hz, J = 0.9 Hz, H6 or H8), 4.83 (1H, d, J = 5.9 Hz, H9b), 3.6-3.75 (1H, m, H2), 2.7-3.1 (3H, m, H2, H3exo, H3a), 1.8-2.3 (1H, m, H3endo).

^{13}CNMR (DMSO-d6) δ 167.89 (C4), 155.48 (C9), 151.26 (C5a), 129.16 (C7), 110.79 (C9a), 108.84 (C6 or C8), 106.84 (C6 or C8), 46.00

(C9b), 40.64 (C3a), 31.16 (C2), 29.37 (C3).

Analysis calc. for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.55; S, 14.43

found: C, 59.63; H, 4.69; S, 14.33.

9-Hydroxy-4,4-dimethyl-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran (17).

Hydroxy-thienolactone (16) (0.67 g, 3.0 mmol) was suspended in ∿ 50 mL dry benzene and added to a ∿ 1 molar solution of methyl magnesium iodide in dry ether prepared from 10 eq each of Mg turninings and methyl iodide. The resultant suspension was stirred at room temperature for 48 hrs, refluxed for 2 hrs, and quenched by the dropwise addition of saturated aqueous ammonium chloride (ice-bath). The organic phase was separated, the aqueous phase extracted with ethyl acetate, and the combined organic phases washed with saturated aqueous sodium chloride and dried overnight (Na_2SO_4). Rotary evaporation gave an oil that contained a significant amount of the starting lactone (TLC, Rf = 0.21, CH_2Cl_2). The oil was taken up in 50 mL dry CH_2Cl_2 and refluxed for 8 hrs in the presence of a catalytic amount of p-TSA. The reaction mixture was then extended with CH_2Cl_2, washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, and dried over sodium sulfate. Mesh chromatography (1 g silica 100-200 mesh as absorbent, 1:1 pet. ether/ether) gave lactone (16) (307 mg), and 203 mg (60% based on recovered lactone) of a red oil from which (17) was obtained by crystallization (MeOH), mp 203-205°C.

TLC Rf = 0.35 (silica, 2:1 pet. ether/ether).

IR (KBr) 3330, 2950, 1605, 1588, 1453, 1235, 1025 cm^{-1}.

^{1}HNMR (DMSO-d6) δ 9.56 (1H, s, OH), 6.84 (1H, t, J = 8.1 Hz, H7), 6.28 (1H, dd, J = 8.1 Hz, J = 1.1 Hz, H6 or H8), 6.17 (1H, dd, J = 8.1 Hz, J = 1.1 Hz, H6 or H8), 4.41 (1H, d, J = 7.9 Hz, H9b), 2.6–2.85 (2H, m, H2), 1.5–2.4 (3H, m, H3, H3a), 1.36 (3H, s, CH_3), 1.17 (3H, s, CH_3).

^{13}CNMR (DMSO-d6) δ 156.19 (C9), 151.75 (C5a), 127.26 (C7), 112.96 (C9a), 107.43 (C6 or C8), 106.89 (C6 or C8), 74.98 (C4), 49.63 (C9b), 31.05 (C3a), 29.42 (C2), 27.69 (C3), 24.82 (CH_3), 12.63 (CH_3).

Analysis calc. for $C_{13}H_{16}O_2S \cdot \frac{1}{4}H_2O$: C, 64.85; H, 6.90; S, 13.29
found: C, 65.04; H, 6.72; S, 13.43.

9-Hydroxy-4,4-dimethyl-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran-S-oxide (18).

Thienobenzopyran (17) (30 mg, 0.13 mmol) was dissolved in 2 mL of methanol. A solution of sodium periodate (30 mg, 0.14 mmol) in 3 mL water was added to (17) all at once and the resultant mixture was stirred at room temperature for 1 hr, then refrigerated overnight. The reaction mixture was diluted with water and extracted with ether to yield 28 mg (87%) of crude (18) which was recrystallized from MeOH/H_2O to provide (18) (18 mg) as off-white crystals, mp 236–239°C with decomposition (sublimes 215–220°C).

IR (KBr) 3416, 2979, 2884, 1591, 1465, 1249, 1215, 1075, 1060, 1042 cm^{-1}.

^{1}HNMR (DMSO-d6) δ 10.05 (1H, s, OH), 6.96 (1H, t, J = 8.2 Hz, H7), 6.39 (1H, dd, J = 8.2 Hz, J = 0.9 Hz, H6 or H8), 6.30 (1H, dd, J = 8.2 Hz, J = 0.9 Hz, H6 or H8), 4.11 (1H, d, J = 7.6 Hz, H9b), 2.8-3.3 (2H, m, H2), 1.6-2.7 (3H, m, H3, H3a), 1.38 (3H, s, C$\underline{H}_3$), 1.17 (3H, s, CH$_3$).

^{13}CNMR (DMSO-d6) δ 156.57 (C9), 154.13 (C5a), 129.05 (C7), 108.08 (C6 or C8), 107.06 (C6 or C8), 103.21 (C9a), 75.53 (C4), 63.12 (C9b), 51.53 (C2), 44.81 (C3a), 27.31 ($\underline{C}$H$_3$), 26.61 (C3), 24.66 ($\underline{C}$H$_3$).

Ms m/z (%) M$^{+\cdot}$252 (46.8), 237 (100), 189 (36.2), 175 (45.3), 161 (52.8), 147 (30.2), 115 (18.0), 91 (28.8), 79 (20.9), 78 (15.1), 77 (44.1), 69 (57.9), 63 (28.7), 59 (9.7), 55 (37.0), 43 (62.8).

Analysis calc. for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39; S, 12.71
found: C, 61.64; H, 6.63; S, 12.58.

5-(1,1-dimethylheptyl)-1,3,dimethoxybenzene (19).

1,1-Dimethylheptyl resorcinol [86] (24.73 g, 0.10 mol), dissolved in 100 mL 2N sodium hydroxide, was treated, under nitrogen, by the dropwise addition of dimethylsulfate (20.8 mL, 0.22 mol) at a rate such that the reaction temperature was maintained between 15° and 20°C. Stirring at room temperature was continued, with the reaction mixture checked by TLC each hour (silica, CHCl$_3$). Sodium hydroxide/dimethyl sulfate, in equi-molar proportions, were added as indicated by TLC. When the reaction was complete, the excess dimethyl sulfate was decomposed (1 hr at reflux). Extraction into ether was followed by successive washes with 1N sodium hydroxide (2X), water (2X) and saturated aqueous sodium chloride (2X). The organic phase was dried over sodium sulfate. Rotary evaporation of solvents, followed by vacuum distillation (125-130°C, 0.2-0.3 Torr, lit.[43] bp. 122°C, 0.5 Torr) gave (19) as a yellow oil (22.3 g, 84.5%).

IR (neat, NaCl) 3080, 2945, 2850, 1590 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 6.49 (2H, d, J = 2.2 Hz, H4, H6), 6.32 (1H, t, J = 2.2 Hz, H2), 3.78 (6H, s, OCH_3), 1.19-1.62 (10H, m, CH_2's), 1.28 (6H, s, gem CH_3's), 0.84 (3H, t, J = 6.2 Hz, H 7′).

^{13}CNMR ($CDCl_3$) δ 160.43 (C1, C3), 152.49 (C5), 104.63 (C4, C6), 96.58 (C1), 55.09 (OCH_3), 44.47 (C1′), 37.94 (C2′), 31.74 (gem CH_3's), 30.00 (C3′), 28.92 (C4′), 24.61 (C5′), 22.64 (C6′), 14.03 (C7′).

Analysis calc. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67
found: C, 77.48; H, 10.90.

2,6-Dimethoxy-4-(1,1-dimethylheptyl)benzaldehyde (20).

Dimethylresorcinol (19), (14.54 g, 55 mmol) was dissolved in 10 mL dry Et_2O and added dropwise to a mixture of 100 mL dry Et_2O and 60 mmol of an n-BuLi solution in hexanes (15 min, nitrogen atmosphere). The reaction was refluxed for 2 hrs, chilled (icebath) and treated by the dropwise addition of dry DMF (5.4 mL, 70 mmol). After 1.5 hrs at room temperature and 1 hr at reflux the reaction was extended with ether and washed successively with saturated aqueous ammonium chloride (2X), water (1X) and saturated aqueous sodium chloride (2X). The organic phase was dried overnight (Na_2SO_4). Purification by flash chromatography (2:1 pet. ether/ ether) gave (20) (7.4 g, 46%) as a pale yellow oil.

TLC Rf = 0.28 (silica, 2:1 pet. ether/ether).

IR (NaCl, neat) 2950, 2920, 2850, 2790, 1675, 1595, 1452, 1238, 1090, 1025 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 10.46 (1H, s, CHO), 6.52 (2H, s, ArH), 3.90 (6H, s, OCH_3), 1.0-1.75 (10H, m, CH_2's), 1.30 (6H, s, gem CH_3's), 0.85 (3H, t, J = 6.2 Hz, term. CH_3).

^{13}CNMR ($CDCl_3$) δ 188.84 (CHO), 161.92 (C2, C6), 159.43 (C4), 112.13 (C1), 101.76 (C5), 55.82 (OCH_3), 44.17 (C1′), 38.99 (C2′), 31.60 (gem CH_3's), 29.81 (C3′), 28.57 (C4′), 24.51 (C5′), 22.50 (C6′), 13.94 (C7′).

Analysis calc. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65

found: C, 74.05; H, 9.57.

2,6-Dihydroxy-4-(1,1-dimethylheptyl)benzaldehyde (21).

Dimethoxyaldehyde (20) (6.48g, 22.2 mmol) was dissolved in 50 mL CS_2 and added as a single portion to a solution of $AlBr_3$ (17.6 g, 3 eq) in 150 mL of carbon disulfide. The red solution was stirred for 3 hrs and quenched by the dropwise addition of 150 mL of 3N hydrochloric acid (ice bath). The CS_2 phase was separated and the solvent removed by rotary evaporation to yield a red oil. The aqueous phase was twice extracted with ether, which was added to the red oil from the CS_2 layer. Washing with saturated aqueous sodium chloride (2X) was followed by drying over sodium sulfate. Purification by flash chromatography (2:1 pet. ether/ether) gave (21) as a yellow oil that turned red on standing (5.64 g, 96%). Elemental analysis was performed on the semicarbazone, mp 231-233, from EtOH.

TLC Rf = 0.46 (silica, 2:1, pet. ether/ether).

IR (NaCl, neat) 3270, 2950, 2920, 2850, 1630, 1600, 1060 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 10.29 (1H, s, CHO), 8.91 (2H, br s, OH), 6.36 (2H, s, ArH), 1.0-1.7 (16H, m, CH_2's, gem CH_3's), 0.84 (3H, t, J = 6.7 Hz, term. CH_3).

^{13}CNMR ($CDCl_3$) δ 193.69 (CHO), 163.38 (C2, C6), 161.24 (C4), 108.34 (C1), 105.60 (C3, C5), 43.96 (C1´), 38.73 (C2´), 33.66 (gem CH_3's), 29.87 (C3´), 28.30 (C4´), 24.56 (C5´), 22.58 (C6´), 13.97 (C7´).

Analysis calc. for $C_{17}H_{26}O_3N_3$: C, 63.72; H, 8.18; N, 13.11
found: C, 63.50; H, 8.42; N, 12.98.

2-Hydroxy-4-(1,1-dimethylheptyl)-6-[tetrahydro-2H-pyran-2-yl)-oxy] benzaldehyde (22).

Dihydroxybenzaldehyde (21) (4.94 g, 18.6 mmol) was dissolved in 50 mL dry CH_2Cl_2 containing 0.45 g (1.9 mmol) of pyridinium tosylate.

Dihydropyran (1.6 g, 19 mmol) was added and the reaction mixture was stirred at room temperature. Dihydropyran was added as required to drive the reaction to completion (TLC, silica, CH_2Cl_2, check for loss of spot at Rf = 0.28). After 4 hrs, the reaction mixture was extended with Et_2O and washed with half saturated aqueous sodium chloride to remove the catalyst, and dried over sodium sulfate. Purification by flash chromatography (CH_2Cl_2) gave (22) as a yellow oil (5.25 g, 81%).

TLC Rf = 0.70 (silica, CH_2Cl_2).

IR (neat, NaCl) 3260, 2960, 2920, 2850, 1640, 1030 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 11.81 (1H, s, CHO), 1033 (1H, s, OH), 6.65 (1H, d, J = 1.5 Hz, H3 or H5), 6.31 (1H, d, J = 1.5 Hz, H3 or H5), 5.52 (1H, br s, H2´) 3.65 (2H, m, H6´), 1.0-2.0 (16H, m, CH_2's), 1.24 (6H, s, gem CH_3's), 0.84 (3H, t, J = 6.2 Hz, term. CH_3).

^{13}CNMR ($CDCl_3$) δ 193.50 (CHO), 162.89 (C2 or C6), 162.54 (C2 or C6), 159.53 (C4), 109.42 (C1), 108.10 (C3 or C5), 103.03 (C3 or C5), 96.61 (C2´), 62.05 (C6´), 43.95 (C1"), 39.03 (C2"), 31.68 (CH_3), 30.11 (CH_3), 29.87 (C3"),28.62 (C3´), 28.30 (C4"), 25.02 (C5´), 24.56 (C5"), 22.58 (C6"), 18.55 (C4´), 14.03 (C7").

Analysis calc. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26
found: C, 72.42; H, 9.48.

Bis-2-[7-(1,1-dimethylheptyl)-3-hydroxy-2-oxo[1]benzopyran-3-yl] ethyl Disulfide (23).

The THP protected aldehyde (22), (4.98 g, 14.3 mmol), and γ-thiobutyrolactone (1.53 g, 15.0 mmol) were dissolved in 2:1 CH_3CN/DMF (60 mL) treated by the addition of 1.45 mL of 1N potassium hydroxide and heated at reflux for 20 hrs. The solvents were then removed by rotary evaporation and replaced with 150 mL of ice-cold water. The vigorously stirred aqueous suspension was adjusted to neutral pH by the dropwise addition of 4N hydrochloric acid (ice bath) and extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium chloride and dried over sodium sulfate. Attempted crystallization of the THP-protected title compound (Et_2O/pet. ether) led instead to the isolation of 150 mg γ-thiobutyric acid disulfide [^1H NMR (DMSO-d6) δ 12.1 (2H, br s, COOH), 2.72 (4H, t, J = 7 Hz, H4), 2.32 (4H, t, J = 7.0 Hz, H2), 1.84 (4H, qt, J = 7.0 Hz, H3)].

Flash chromatographic purification (3:1 pet. ether/ether) gave 3.80 g (62%) of the crude THP-protected disulfide [^1H NMR ($CDCl_3$) δ 7.9 (1H, s, H4′), 6.85-7.05 (2H, m, H6′, H8′), 5.55 (1H, br s, H2"), 3.45-4.0 (2H, m, H6"), 3.0 (4H, br s, H1, H_2), 1.0-2.05 (16H, m, other CH_2's), 1.3 (6H, s, gem CH_3's), 0.84 (3H, t, term. CH_3)]. Deprotection (EtOH, PPTS, 55°C, 7 hrs) [60] gave disulfide (23) in near quantitative yield following flash chromatography (1:1 pet. ether/ether), mp. 164-166°C.

TLC Rf = 0.41 (silica, 1:1 pet. ether/ether).

IR (KBr) 3340, 2923, 2854, 1678, 1621, 1570, 1421, 1287, 1062 cm^{-1}.

^{1}HNMR (DMSO-d6) δ 10.48 (1H, s, OH), 7.92 (1H, s, H4´), 6.74 (2H, s, H6´, H8´), 2.92 (4H, m, H1, H2), 1.0-1.7 (10H, m, H2" → H6"), 1.23 (6H, s, gem CH_3's), 0.80 (3H, t, J = 5.3 Hz, H7").

^{13}CNMR (DMSO-d6) δ 160.96 (C2´), 154.19 (C7´), 153.75 (C5´, C8a´), 135.39 (C4a´), 122.77 (C4´), 107.60 (C6´or C8´), 103.97 (C6´ or C8´), 43.56 (C1"), 37.82 (C1 or C2), 35.71 (C1 or C2), 30.18 (gem CH_3's), 29.26 (C3"), 28.39 (C4"), 24.12 (C5"), 22.00 (C6"), 13.77 (C7").

Analysis calc. for $C_{40}H_{54}O_6S_2$: C, 69.13; H, 7.83; S, 9.23
found: C, 69.28; H, 7.91; S, 8.99.

9-Hydroxy-7-(1,1-dimethylheptyl)-2,3,3a,9b-tetrahydrothieno[3,2-c]-[1]benzopyran-4-one (24).

THP protected aldehyde (22), (2.29 g, 6.6 mmol), γ-thiobutyrolactone (0.68 g, 6.6 mmol) and 30 mL dry DMF were charged into a 3-neck reaction vessel and de-oxygenated by bubbling N_2 directly into the solution while stirring (0.5 hr). Potassium carbonate (1.5 g, finely divided, dried under vacuum) was added under a nitrogen atmosphere. The reaction mixture was stirred vigorously at 80°C for 8 hrs (nitrogen, constant temperature bath). Separation of the potassium carbonate, followed by rotary evaporation of the solvent gave a red oil which was suspended in 100 mL ice-cold water. The resultant suspension was stirred vigorously and adjusted to neutral pH by the dropwise addition of 3N hydrochloric acid (ice bath). Extraction with equal portions of ether and ethyl acetate was followed by washing the combined organic phases (saturated aqueous sodium chloride) and drying over sodium sulfate. ^{1}HNMR examination of this crude material showed it to be a mixture of the desired THP-thieno/-lactoneand the THP protected disulfide. This crude mixture was deprotected (EtOH, PPTS, 55°C, 6 hrs) [60], and purified by mesh chromatography (4 g 100-200 mesh silica as absorbant, 9:1 CH_2Cl_2/pet. ether) to yield 0.97 g (42%) of (24) as a white crystalline solid, mp 145-146.5°C.

TLC Rf = 0.38 (silica, 9:1 CH_2Cl_2/pet. ether).

IR (KBr) 3411, 2922, 2853, 1733, 1631, 1594, 1439, 1259, 1238, 1045 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 6.62 (2H, br s, H6, H8), 5.84 (1H, br s, OH), 4.91 (1H, d, J = 5.9 Hz, H9b), 2.9-3.45 (4H, m, H2, H3endo, H3a), 1.9-2.4 (1H, m, H3exo), 1.0-1.7 (10H, m, H2′ → H6′), 1.22 (6H, s, gem CH_3's), 0.84 (3H, t, J = 5.4 Hz, H7′).

^{13}CNMR ($CDCl_3$) δ 168.55 (C4), 153.39 (C5a or C9), 152.84 (C5a or C9), 151.11 (C7), 109.29 (C6 or C8), 107.18 (C6 or C8), 105.77 (C9a), 46.83 (C9b), 44.33 (C1′), 40.98 (C3a), 37.89 (C2′), 31.93 (C2), 31.77 (gem CH_3's), 30.19 (C3), 29.98 (C3′), 28.73 (C4′), 24.61 (C5′), 22.66 (C6′), 14.05 (C7′).

Analysis calc. for $C_{20}H_{28}O_3S$: C, 68.93; H, 8.10; S, 9.20

found: C, 68.85; H, 8.36; S, 9.15.

Elaboration of tetrahydrothienolactone (24) to THC analogs:

Lactone (24), (1.05 g, 3.0 mmol) was taken up in 40 mL dry benzene and added to an approximately 1 molar ethereal solution of methyl Grignard, prepared from 10 eq. each of Mg turnings and methyl iodide. The reaction mixture was stirred at room temperature for 18 hrs, refluxed for 2 hrs, and quenched by the dropwise addition of saturated aqueous ammonium chloride (ice bath). Extraction with ether was followed by drying of the organic phase (saturated aqueous sodium chloride wash, then storage over sodium sulfate). Rotary evaporation of the solvents provided the crude triol as a golden oil in near quantitative yield [^{1}HNMR ($CDCl_3$) δ 8.25 (2H, br. s, ArOH), 6.5 (2H, s, ArH), 5.15 (1H, d, J = 6.1 Hz, H2), 1.0-3.3 (15H, m, H3, H4, H5, H2′ → H6′), 1.35 (3H, s, $C\underline{H}_3$-C-OH), 1.2 (6H, s, gem CH_3's), 0.85 (3H, t, H7′), 0.75 (3H, s, $C\underline{H}_3$-C-OH)].

This material was further dried by azeotropic removal of water (CH_2Cl_2, rotary evaporation, 2X), taken up in 40 mL dry CH_2Cl_2 containing a catalytic amount of p-TSA, and refluxed for 8 hrs. The reaction mixture was extended with ether, washed with saturated aqueous sodium bicarbonate (2X) and saturated aqueous sodium chloride (1X), and dried over sodium sulfate. Rotary evaporation of the solvents followed by flash chromatography (9:1 CH_2Cl_2/pet. ether) gave a golden oil (0.73 g, 67%), that, by ^{1}HNMR, was predominantly thienobenzopyran (25). (9:1 *cis* to *trans* by integration of the H9b proton resonances). Attempts to purify this oil by column chromatography met with failure, but a crystalline material could be obtained from Et_2O/pet. ether. This crystalline compound (170 mg) was purified by flash chromatograph (19:1 $CHCl_3$/MeOH) to yield:

9-Hydroxy-4,4-dimethyl-7-(1,1-dimethylheptyl)-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran (25).

TLC Rf = 0.83 (silica, 19:1 $CHCl_3$/MeOH) 10 mg.

^{1}HNMR ($CDCl_3$) δ 6.41 (1H, d, J = 2.0 Hz, H6 or H8), 6.37 (1H, d, J = 2.0 Hz, H6 or H8), 5.70 (1H, br s, OH), 4.48 (1H, d, J = 6.7 Hz, H9b), 2.85-3.05 (2H, m, H2), 1.0-2.5 (13H, m, H3, H3a, H2´ → H6´), 1.45 (3H, s, C4-C$\underline{H}_3$), 1.31 (3H, s, C4 C$\underline{H}_3$), 1.20 (6H, s, C1´-C$\underline{H}_3$'s), 0.84 (3H, t, J = 5.9 Hz, H7´).

^{13}CNMR ($CDCl_3$) δ 154.74 (C5a or C9), 151.98 (C5a or C9), 151.06 (C7), 107.93 (C9a), 107.72 (C6 or C8), 106.95 (C6 or C8), 75.21 (C4), 51.81 (C9b), 44.28 (C1´), 40.87 (C3a), 37.40 (C2´), 31.71 (C1´-C$\underline{H}_3$'s), 30.36 (C3), 29.92 (C3´), 28.62 (C4´), 28.08 (C4-$\underline{C}H_3$), 25.51 (C4-$\underline{C}H_3$), 24.51 (C5´), 22.67 (C6´), 14.00 (C7´).

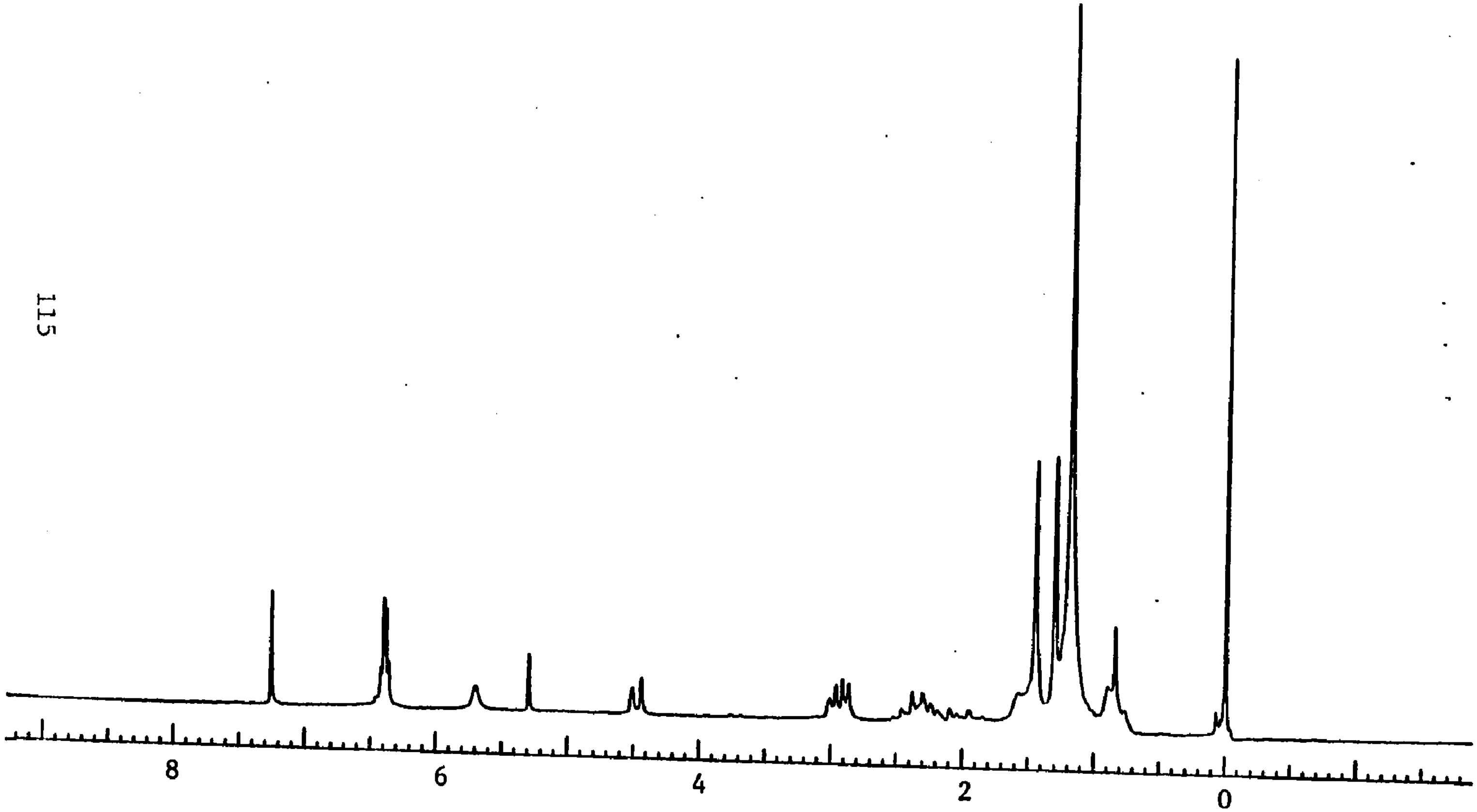


Figure 24: ^{1}HNMR spectrum of 9-Hydroxy-4,4-dimethyl-7-(1,1-dimethylheptyl)-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran.

9-Hydroxy-4,4-dimethyl-7-(1,1-dimethylheptyl)-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran-S-oxide (26).

TLC Rf = 0.52 (silica, 19:1 $CHCl_3$/MeOH) mp 214-216°C (150 mg) white plates.

IR (KBr) 3056, 2924, 2812, 1616, 1577, 1414, 1288, 1228, 1069, 1055 cm^{-1}.

^{1}HNMR ($CDCl_3$) δ 9.15 (1H, br s, OH), 6.48 (1H, d, J = 1.5 Hz, H6 or H8), 6.30 (1H, d, J = 1.5 Hz, H6 or H8), 4.41 (1H, d, J = 8.2 Hz, H9b), 3.3-3.6 (1H, m, H2), 1.0-3.2 (14H, H2, H3, H3a, CH_2's), 1.43 (3H, s, C4-$C\underline{H}_3$), 1.28 (3H, s, C4 $C\underline{H}_3$), 1.18 (6H, s, C1′-$C\underline{H}_3$'s), 0.83 (3H, t, J = 6.5 Hz, H7′).

^{13}CNMR ($CDCl_3$) 156.28 (C5a or C9), 153.41 (C5a or C9), 152.82 (C7), 106.58 (C6 or C8), 106.12 (C6 or C8), 99.91 (C9a), 75.46 (C4), 64.16 (C9b), 51.78 (C2), 45.69 (C1′), 44.36 (C3a), 37.64 (C2′), 31.71 (C1′-CH_3's), 29.92 (C3′), 28.62 (C4′), 27.02 (C4-$\underline{C}H_3$), 25.26 (C4-$\underline{C}H_3$), 24.56 (C5′), 22.61 (C6′), 14.05 (C7′).

MS m/z (%) $M^{+\bullet}$378 (20.2), 363 (100), 329 (1.6), 315 (27.2), 301 (8.6), 293 (< 1), 278 (<1), 260 (<1), 91 (25.3), 79 (18), 77 (21.4), 69 (41), 63 (23.2), 59 (7.7), 55 (55.9)

Analysis calc. for $C_{22}H_{34}O_3S$: C, 69.80; H, 9.05; S, 8.47
found: C, 69.67; H, 9.19; S, 8.61.

Alternate preparation of:

9-Hydroxy-4,4-dimethyl-7-(1,1-dimethylheptyl)-2,3,3a,9b-tetrahydrothieno[3,2-c][1]benzopyran-S-oxide (26).

The crude sulfide (25) (123 mg, 0.34 mmol) was dissolved in 15 mL methanol and treated by the addition of sodium periodate (73 mg, 0.34 mmol) in 5 mL water. The reaction mixture was stirred for 1 hr and refrigerated overnight. Rotary evaporation of most of the methanol was followed by dilution of the reaction mixture with water. Extraction of this aqueous mixture with ether and CH_2Cl_2 gave an oil which was crystallized from a small amount of ether to give 70 mg (61%) of (26), indistinguishable by spectral means from the material described above.

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