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Investigations of Cannabinoid
Synthesis : Chromenes

University — Université

CARLETON U.

Degree for which thesis was presented — Grade pour lequel cette thèse fut présentée

M.Sc. CHEM.

Year this degree conferred — Année d'obtention de ce grade

Jan 1982

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INVESTIGATIONS OF
CANNABINOID SYNTHESIS:
CHROMENES

by
Lee W. Herman

A thesis submitted to the
Faculty of Graduate Studies
in partial fulfilment of the
requirements for the degree of
Master of Science

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January 1982

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in partial fulfilment of the requirements for
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ABSTRACT

The synthesis of the chromene Δ^3 -2,2-dimethyl-5-hydroxy benzopyran (103) was undertaken, in an attempt to study a proposed novel base catalyzed alkylation for the construction of the C-ring of the cannabinoid skeleton. Chromanone 118, formed by the pyrrolidine catalyzed condensation of 2,6-hydroxy acetophenone and acetone, was reduced to chromanol 123 and the phenol-protected as the phenacyl ether (125). Dehydration, followed by phenol regeneration, gave the chromene 103 in good yield. However, NMR studies failed to show the formation of the reactive species necessary for the desired alkylation. Chromene 103 was also unreactive in a Diels-Alder sense.

Other alkylations at C-3 of chromanone 140 were investigated. An undesirable aromatic substitution, under acidic conditions, was encountered, as well as the elucidation of an appropriate base catalyzed alkylation with an allylic halide using LiH in the presence of HMPA. This reaction could be useful in the total synthesis of 7-oxo cannabinoids.

ACKNOWLEDGEMENTS

I would like to thank Dr. John ApSimon for his remarkable patience and encouragement. Also uniquely valuable were discussions with my friends of the laboratory, who were a constant source of consultation and amusement.

I would also like to thank Mr. Karl Diedrich, who was instrumental in the acquisition of lab supplies, and Mrs. Marilyn Stock for the typing of this thesis.

In addition, I am grateful to the Department of Chemistry, Carleton University, and again to Dr. ApSimon for funding throughout the project period.

TABLE OF CONTENTS

Abstract	i
Acknowledgements	ii
Table of Contents	iii
Foreword	iv
Introduction	
A) Cannabinoids: An overview	1
B) Chromenes: Biological Activity	9
C) Chromenes: Synthetic Strategies	14
Results and Discussion	29
Synthesis of 7-OH Chromenes	30
Synthesis of 5-OH Chromenes	32
Synthesis of 5,7-dihydroxy-4-chromanones	39
Suggestions for future research	50
Experimental	51
References	85

FOREWORD

Structural formulae representing synthetic materials containing asymmetric centers depict only one enantiomer but refer to racemic mixtures throughout. In the text the ($\pm$) prefix is omitted for convenience.

The following is a representation of the benzopyran numbering system used in the text:

Introduction

A) Cannabinoids : An overview

In this chapter, the class of compounds known as the cannabinoids will be introduced in terms of their potential uses in contemporary society and synthetic schemes will be touched on. Then, a new class of insecticides called chromenes will be examined, as they represent possible starting material for cannabinoid synthesis. The biological activity and synthesis of chromenes will be presented in some depth.

The term cannabinoids refers to the class of compounds commonly found in the plant Cannabis sativa. The major physiologically active component is (+)- Δ^9 -3,4-trans-tetrahydrocannabinol (THC) (1).

The use of cannabis was widespread in ancient Chinese, Indian and Middle Eastern medical lore for the treatment of insomnia, neuralgia, migraine pain, rheumatism, asthma, bronchitis, loss of appetite,

2.

and gynecological and obstetrical problems. It is still used in Aynvedic and Tildoi systems, of Indian medicine.

The great increase in cannabis use among Western cultures in the 1960's had tremendous sociological impact. A vast number of studies have examined the effect of THC on human biology (i.e. metabolism, enzyme systems, hormonal effects, gross morphological effects) and psychology (learning, perception, suggestibility affect, communication), but the conclusions that may be drawn are controversial, to say the least.

Pharmacologically, the most prominent effects of Δ^9 -THC are decreased locomotor activity, increased sensitivity to external stimuli such as sound and touch ("popcorn effect"), general depression and at high doses, static and dynamic ataxia. As a class of compounds, however, the cannabinoids are extraordinary in the degree that the pharmacological effects may be separated through structural variation, while still maintaining their low toxicity. This has led to the development of a number of cannabinoid drugs. Illicit use of cannabis among patients on cancer chemotherapy suggested their value as effective combatants of nausea associated with this kind of treatment. Some synthetic anti-nausea cannabinoid-like compounds include Nabilone (2) Nabitan (3), and A-41988 (4)⁴.

Cannabinoids characteristically possess analgesic activity. This potential has been shown for both (Δ^1)-THC⁵ and Nabitan^{6,7}. Nantradol (5) has been shown⁸ to be 9-30 times more potent than morphine as an analgesic. It is unique in that it does not seem to bind to opiate receptors, as it is not antagonized by Naloxone. This suggests that it would not cause the usual opiate dependence, instead it is postulated that it operates through some effect on prostaglandin metabolism.

In 1974, it was shown⁹ that DMHP (6) has hypotensive action at doses too low to show CNS effects. Nabilone has shown promise as a tranquilizing agent¹⁰ and Δ^9 -THC has been used as an antiasthmatic³ and an appetite stimulator¹². There are clinical indications¹⁴ that cannabis may alleviate some of the symptoms of epilepsy, and great interest has been placed on Δ^9 as an agent for reducing intraocular pressure of the eye in sufferers of glaucoma¹⁴. Research in animal physiology has shown potential for cannabinoids as antiinflammatory, antipyretic, antitussive, antispasmodic, antidiarrheal, sedative-hypnotic, antidepressant, anti-cancer and antialcoholic agents.

Since the first total synthesis of Δ^9 -THC by Mechoulam and Gaoni¹⁵ in 1965, a great number of syntheses have been published. The most widely used approach involves the condensation of a monoterpenoid moiety with

olivetol in the presence of an acid catalyst followed by cyclization of the benzofuran ring (Figure 1)¹⁶. Using the steroid convention of ring notation this represents an A + C → AC → ABC approach.

A much less exploited approach is the A → AB → ABC approach. In 1967, Fahrenholtz (Figure 2) and co-workers¹⁷ pioneered this approach. The von Pechmann condensation

FIGURE 1

of olivetol and diethyl α -acetoglutarate (8) in the presence of phosphoryl chloride afforded only one coumarin 9. C ring cyclization was effected by treatment with NaH in DMSO. After protection of the ketone as its ethylene ketal, the coumarin was treated with MeMgI, whereupon treatment with acid re-cyclized ring B, regenerated the C-ring ketone, and moved the C-6a double bond into conjugation with the ketone. Reduction of the double bond with Li/NH₃ afforded the natural trans ring junction (11).

FIGURE 2

The synthesis of Nabilone (2) was achieved by Archer et al¹⁸ in 1976 using the same method.

Fahrenholtz also synthesized the C-ring ketone via a 2,3-dimethyl chromanone (Figure 3). Condensation of olivetol with 3,3-dimethyl acrylic acid (13) gave a mixture of the "natural" 3-pentyl (14) and the "unnatural" 1-pentyl (15) chromanones. After separation, treatment of 14 with ethyl formate and NaH gave the hydroxymethylene derivative 16 which underwent a Robinson annelation upon treatment with MVK in the presence of triethylamine, to give the ketocannabinoid (11).

FIGURE 3

An unexplored $A \rightarrow AB \rightarrow ABC$ approach involves the use of an intermediate 2,2-dimethyl chromene system such as 17 (Figure 4). If alkylation at C-3 would occur, then cyclization would yield the saturated C-ring ketone system with a trans ring junction without the need for a stereoselective reduction.

FIGURE 4

In addition, chromene 17 could be used as a Diels Alder precursor. In 1977, Handrick and co-workers¹⁹ (Figure 5) formed the C-ring by Diels Alder reaction of coumarin 18 with isoprene to give the cis ring junction coumarin 19. Since the cis ring junction may be isomerized to the trans using $AlCl_3$ ¹⁸, this represents a useful route.

FIGURE 5

Other examples of C-ring formation are syntheses by Jen et al²⁰ who condensed an olivetol cinnamic acid (20) with 2-methyl-1,3-butadiene (Figure 6) and Kochi and Matsui²¹ who reacted MVK with the appropriate diene 24 to give the ketone 25 (Figure 7).

FIGURE 6

B) Chromenes : Biological Activity

Recently a class of chromene known as precocenes have emerged as potential fourth generation insecticides. In 1961 Schmialek²² showed the activity of farnesol (26) and farnesal (27) as juvenile hormones (JH). JH's affect

FIGURE 7

biological processes which are unique to insects. In man, adult development is triggered by hormones such as hypophyseal gonadotropins, while in insects JH's prevent the development of larva to adults; they (ie. the JH's) must be absent during metamorphosis. If JH is applied to an insect during metamorphosis, an insect with both adult and juvenile characteristics results and this "mosaic" insect cannot feed, mate, or reproduce²³. After metamorphosis, the insect again produces JH's. In addition, a lack of JH's during adult life induces a condition, the diapause state, where the insect does not feed or mate in order to withstand adverse conditions. JH's have also been shown to be responsible for ovarian development and the release of sex attractants.

26 27 28 R=Me29 R=H 30 31 32

Thus it is clear that JH's themselves are not practical as an insecticide, since they would have to be applied exactly during metamorphosis. However, if JH production were interrupted before metamorphosis, the insect would develop precosiously to an adult. This adult couldn't reproduce due to lack of eggs, would be thrown into a state of diapause unnecessarily, or would not produce sex attractants.

Farnasol was shown by Judy and co-workers²⁴ to be a natural JH in tobacco hookworm, while, from cecropia other JH's were isolated^{25,26} (28,29). The development of JH analogs with aromatic moieties, found to be at least 1000 more potent than the natural JH's^{25,26} (30,31), led to Methoprene²⁷ (32) which is used for floodwater mosquito control and for the control of flies that breed on manure.

In 1976, Bowers²⁸ isolated two compounds from the plant Ageratum houstonianum which caused precocious metamorphosis, prevented ovarian development, and induced diapause. These compounds, which he called Precocene 1 (33) and Precocene 2 (34) were already known as 6-demethoxy ageratochromene²⁹ and ageratochromene³⁰ by the groups who had characterized them. Later, Bowers and Pratt³¹ showed that Precocene II acted by the suppression of endogenous JH's, and Pever and co-workers³² subsequently demonstrated that this suppression was due to atrophy of the corpora allata (CA), the organ responsible for the synthesis of JH's in insects.

The metabolism of Precosene II was studied by Bowers and co-workers³³⁻³⁶ who hypothesized the existence of an active epoxide metabolite, which was isolated as a diol after reaction with water, as well as o-demethylated and hydrated products (Figure 8). Chromene epoxides have been shown to be very reactive to nucleophiles^{36,37} giving cis-diols by a proton catalyzed ring opening or trans diols by a nucleophilic mechanism. Pratt and co-workers³⁸ showed that certain insects may be protected from the action of Precocene by treatment with mixed function oxidase inhibitors, supporting the theory of metabolic activation. Later they demonstrated³⁹ the

FIGURE 8

covalent attachment of labelled Precocenes in the CA,
and the concentration of diols in that same organ.

However, in 1980 Bergot and co-workers⁴⁰ showed that in some insects the 6- and 7-O- β glucopyranosides (41, 42) were the major metabolites, rather than the diols, which sheds doubt on the actual mechanism of action of the Precocenes.

Vyas and Mulchandani⁴¹ examined the biosynthesis of Precocenes I and II. Using labelled acetate and mevalonic acid it was shown that the acetate moiety carbons become the aromatic nucleus, while the mevalonic acid accounts for the activity of the radioactivity of one of the gem-dimethyls. They suggest that the aromatic ring condenses with

dimethyl allyl pyrophosphate arising from mevalonic acid:

C) Chromenes : Synthetic Strategies

The synthesis of 2,2-dimethyl chromenes may be approached either by the preparation of another related ring system with subsequent variation of functionality

or by alkylation of a free phenol followed by cyclization onto the aromatic ring. Among the former, the earliest approach was the alkylation of a coumarin with a Grignard reagent⁴². In 1907, Fellenberg and Decker⁴³ showed that the mechanism involves an intermediate pyrilium salt (45) which was isolated after neutralization with HCl (Figure 9).

The most popular route to 2,2-dimethyl chromenes uses the 4-chromanone system as an intermediate. The first example was published by Beneze and co-workers⁴⁴ who synthesized 2,2-dimethyl-5,7-dimethoxy-3-chromene by reduction of the chromanone with LAH followed by dehydration with phosphoryl chloride in pyridine (Figure 10). Other dehydration agents used have included HCl^{45,46}, p-toluene sulphonic acid⁴⁷, and aluminum oxide⁴⁸. Not all 4-chromanols may be dehydrated under acidic conditions, however. On

FIGURE 9

FIGURE 10

the basis of results by Livingstone and Whiting⁴⁹, Fukami and co-workers⁵⁰ reported the synthesis of dimer 50 by letting 51 stand in 20% H₂SO₄. This same group also reported the synthesis of intractable red resins in the attempted demethylation of 51 with HI or aluminum chloride. Kasturi and Manithomas⁵¹ isolated a dimer of Precocene II and based on NMR data assigned structure

52

52. Schwartz⁵² confirmed this synthesis and showed that Precocene I does not dimerize in an analogous fashion, but polymerizes.

The synthesis of 2,2-dimethyl-4-chromanones may be accomplished by two general methods. The simplest is the condensation of an α,β -unsaturated acid with a phenol in the presence of an acid catalyst (Figure 11). Successful catalysts have been HF ⁵³, antimony chloride⁵³, a mixture of zinc chloride and phosphoryl chloride⁵⁴, polyphosphoric acid⁵⁵, BF_3 etherate⁵⁶, and methane sulphonic acid⁵⁷, the reagent of choice. Condensation with resorcinol affords only the 7-OH regioisomer. Alternately, the 4-chromanone system may be synthesized via the appropriate o-hydroxy acetophenone. Aldol condensation with acetone in the

FIGURE 11

FIGURE 12

presence of bases (Figure 12) such as LDA⁵⁸ or pyrrolidine⁵⁷ affords the chromanone in generally good yields.

The 2,2-dimethyl chroman system is another widely used precursor to chromene systems. Early syntheses started with the corresponding 4-chromanone system, reducing the ketone under Clemmensen conditions⁶⁰ or with diborane⁶¹. Gujral and Gupta⁶², in their synthesis of 6-desoxyjacareubin (**58**) and 6-desoxyisojacareubin (**59**), formed a chroman ring system by prenylation of an aromatic intermediate **60** with 2-methylbut-3-en-2-ol (Figure 12a) in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. This method was also successfully used by Jain and co-workers⁶³ in their synthesis of lupinifolin (**62**). Jain and co-workers⁶⁴

FIGURE 12a

in their synthesis of the carpachromene 63, prenylated the aromatic precursor with dimethylallyl bromide in the presence of sodium methoxide and, working with still another group⁶⁵, elaborated a route to pomiferin (64) using virtually identical conditions. The dihydro derivative of alloevodionol- (65) was synthesized by Cardillo et al⁶⁶ by prenylation of the aromatic nucleus with dimethylallyl bromide and n-BuLi. Steelink and Marshall⁶⁷ prenylated 1-acetyl-2,4-dihydroxybenzene with 2-methyl-3-en-ol and formic acid, but only obtained a 7% yield. Recently Tachibana⁶⁸ introduced a novel metal resin catalyst which he showed to be effective for the production of 7-OH chroman systems from resorcinol and allylic bromides..

Camps and co-workers⁷⁶ investigated bis-[acetylacetonato]-nickel as a catalyst for the condensation of phenols with 1,3-dichloro-3-methyl butane (83), a stable and readily available material. In their hands the reaction of resorcinol monomethyl ether (82) and 83 gave a 65% yield of 7-methoxy-2,2-dimethyl chroman (84) and 5-methoxy-2,2-dimethyl chroman (85) as a 2:1 mixture (Figure 16).

Formation of the chromene system from its corresponding chroman may be effected by halogenation-dehydrohalogenation or hydride abstraction..

FIGURE 16

Fukami and Nakajima⁶⁰ used NBS in CCl_4 to benzylically brominate the acetate ester of 5-hydroxychroman, and then dehydrobrominated with triethanolamine. By far the most used method, however, is hydride abstraction with DDQ^{66,62,70,65,64,63}. Meikle and Stevens⁷¹ found this reaction sensitive to substitution on the aromatic ring. Attempts to synthesize 5,7-dihydroxy-3-chromene by this route were unsuccessful as any phenol protecting group which could be removed under conditions which would not affect the chromene system (e.g. acetyl, benzoyl, tosyl) prevented any reaction from occurring. These workers noted that since no deep colouration was formed in solution after addition of DDQ, a charge transfer complex was not forming. They blamed reduced electron density on the aromatic nucleus as the primary factor, and considered steric factors to be relatively unimportant.

FIGURE 13

Alternately, the prenylated aromatics may be directly cyclized to a chromene system. Cardillo and co-workers⁶⁹ reported the reaction of ortho-prenyl phenols with potassium dichromate in benzene in the presence of a phase transfer catalyst, Adogen 464. They proposed an intermediate chromate ester (67) which decomposes to an o-quinoneallide (68), followed by cyclization (Figure 13). He also described the same reaction using DDQ (70) in diethyl ether. In 1979, Bongini and co-workers⁷² described the same cyclisation with *n*-iodosuccinimide

70

FIGURE 14

(Figure 14). This method is unsuccessful, however, with materials where the aromatic ring has many electron donating groups, facilitating ring iodination. The attempted synthesis of Precocene I, however, gave the correct material in 82% yield.

After having observed that citral reacts with *m*-dihydroxy phenols, with one of the hydroxyls chelated, to give chromenes, Crombie and co-workers synthesized a variety of 2,2-dimethyl chromenes using the synthon 3-hydroxy-3-methyl-1,1-dimethoxy butane (**73**). For example, reaction of **73** with 2,4-dihydroxyacetophenone in pyridine gives a 59% yield of 6-acetyl-5-hydroxy-2,2-dimethyl chrom-3-ene. Using this method, this group

easily synthesized evodionol 7-methyl ether (74), and jacareubin (75). 73 does not significantly dehydrate in pyridine at the reaction temperatures (90% recovered after 48 hrs), so the reaction probably does not proceed through 3-methyl-but-2-enal dimethyl acetal. Camps and co-workers⁷⁴ used this method to produce the trifluoromethyl analogue of Precocene II (76), using acetal 77.

The mesylate was necessary to offset the increased carbon-oxygen bond strength due to the trifluoromethyl group. Sartori and co-workers⁷⁵ reacted metal phenolates with α,β -unsaturated aldehydes and ketones in toluene and obtained good yields of chromenes. Titanium, magnesium, tin and aluminum phenolates were all found to be reactive species, but highly co-ordinating solvents (e.g. DMF,

FIGURE 15

glyme, HMPA, TMEDA) causes failure of the reaction. The reaction is highly regioselective. The condensation of olivetol (78) with 3-methyl-2-butenal (71) gives the "unnatural" 5-pentyl isomer in 77%, and only 3% of the "natural" 7-pentyl isomer (Figure 15).

In 1962, Iwai and Ide⁷⁶ first reported the synthesis of chromenes from the Claisen rearrangement of propargyl aryl ethers. Hlubeczek and co-workers⁷⁷ developed syntheses of Precocene I and II; O-alkylation of 3-methoxy or 3, 4-dimethoxy phenol with 3-chloro-3-methyl-1-butyne in acetone in the presence of potassium carbonate, followed by cyclization in N,N-diethylaniline, gives the chromenes in 70-90% yield (Figure 16). Ansari and co-workers⁷⁸ used

FIGURE 16

this method starting with 2-hydroxy-4,6-ditosyloxy acetophenone (89) and got only the 8-acetyl chromene (90) (Figure 17) as product, without any rearrangement to the 6-acetyl derivative, as was reported in similar cases^{79,80}. As well, C-propargylation was inhibited, as described for phloroacetophenone⁸¹ (91) and 2-hydroxy-4-methoxy acetophenone⁸² (92). Ahluwalia and co-workers⁸³ synthesized

FIGURE 17

various linear pyranocoumarins, controlling the cyclisation of the chromene with a blocking group which could be later removed. Thus, reaction of 7-hydroxy-5-methoxy coumarin (93) with iodine/periodic acid gave the 8-iodo derivative 94, which was O-alkylated with 3-chloro-2-methyl-1-butyne. Refluxing in DMF cyclized and eliminated iodide, giving xanthoxyletin (96) in about 27% yield from 93 (Figure 18).

FIGURE 18

Begasse and Le Corre⁸¹ synthesized a variety of chromenes from *o*-hydroxybenzyl triphenylphosphonium salts and α -halo carbonyl compounds in the presence of base (Fig. 19). Yields were moderate.

FIGURE 19-

Results and Discussion

To investigate the synthetic utility of the approach outlined in Figure 4, a chromene hydroxylated in the five position, such as 17, was required. 2,2-dimethyl-5-hydroxy chromene (103) was chosen as a model compound and its synthesis undertaken. The initial approach is outlined in Figure 20. The formylation of 104 occurred in 40-50% yield, but this reaction has been improved by the use of DMF⁸⁵ as the formylating agent. Reaction of 105 with the stable phosphorane⁸⁶ 106 occurred cleanly in high yield. However, the one pot Grignard fusion methylation and dealkylation¹⁵ gave only about 30% of the desired

FIGURE 20

product. Although this route would provide enough material for any desired model studies, it was unsatisfactory for a multistep cannabinoid total synthesis; alternate methods were required. Low yields also plagued the syntheses of 103 and its methyl ether 51 devised by Fukami and co-workers⁵⁰, and so it was not considered further. However, their work clearly demonstrated that selection of the appropriate phenol protecting group was paramount, since it had to withstand a variety of reaction conditions and yet be removed by conditions which would not disturb the labile chromene double bond.

Synthesis of 7-OH chromenes - A Model System

As a first attempt, the tosyl group was used to protect the phenol on the readily available chromanone

FIGURE 21

system 108 (Figure 21). Generation of the chromene system was possible in a simple fashion, the only problem being the loss of a small amount ($\sim 20\%$) of the chromanol 110 due to competing detosylation by LAH. However, hydrolysis of the tosyl group did not occur on treatment with KOH and only tars were isolated; photochemical cleavage was also ineffective.⁸⁷ In addition, reaction of 111 with the Danishefsky⁸⁸ diene 1-methoxy-3-trimethylsilyloxy-1,3-butadiene failed to give any Diels-Alder adduct.

Several rather simple routes to the 7-OH chromene were attempted. In the first of these (Figure 22), 113 was synthesized in 50% yield but gave only tars on reaction with DDQ. The second was an attempt to react resorcinol

FIGURE 22

(53) with 73 despite the absence of a chelated hydroxyl in 53 (Figure 23); no reaction was detected.

As the methodology for the synthesis of 5-hydroxylated chromanones was developed in parallel studies, work on this series of compounds was discontinued.

Synthesis of 5-OH Chromenes

Since the reaction of β,β -dimethyl acrylic acid with resorcinol gives only the 7-OH chromanone, a method of insuring the correct 5-OH regioisomer was necessary. Formylation such as was described earlier was not likely using unprotected phenols. However, it is possible to synthesize, in high yields, 2,6-dihydroxyacetophenone (117) from resorcinol via

FIGURE 23

the appropriately substituted coumarins⁸⁹ (114 $\rightarrow$ 116, Figure 24). Cyclization to the chromanone (118) with pyrrolidine and acetone using conditions developed by Kabbe⁵⁹ occurred cleanly in $\sim 75\%$ yield (Figure 25).

FIGURE 24

FIGURE 25

In view of the strong chelating effect shown by ortho-hydroxy aromatic ketones, an attempt was made to introduce the tosyl group on the phenol under anhydrous phase transfer conditions (powdered KOH, tetrabutylammonium bromide and p-toluene sulphonyl chloride in THF)⁸⁹. The reaction occurred smoothly. Reduction to the chromanol did not occur with NaBH_4 or KBH_4 under phase transfer conditions⁹⁰, and treatment with LiAlH_4 produced only the deprotected chromanol.

Since introduction of the tosyloxy group proved unsatisfactory, the acetyl group was next tried as the phenol protecting group since Matsui and co-workers⁵³ have reported the liberation of OH chromenes from the acetylated counterpart under mild saponifying conditions. However, standard acetylating conditions (acetic anhydride, pyridine) failed to produce a protected product: anhydrous phase transfer conditions gave the desired product in excellent yield.

Reduction to the corresponding chromanol with NaBH_4 failed, and in light of the lability of the acetate group to reducing conditions, this route was discarded.

Reduction of the benzyl ether of a 5-OH chromanone had been reported⁵⁰, and so this approach was next tried in the hope that sufficiently mild conditions

could be found for deprotection. After benzyl chloride failed to react with the phenol 118 (Figure 26) under standard alkylating conditions, the bromide proved satisfactory. Reduction of 120 with NaBH_4 occurred readily, as did the subsequent dehydration with p-toluene sulphonic acid. Compound 122, however, proved to be an unsuitable synthetic intermediate since catalytic hydrogenation over palladium-charcoal using less than one equivalent of hydrogen yielded only deprotected chroman and unreacted starting material. Subsequent attempts at dealkylation using a wide variety of reagents noted for their mildness all failed⁹²⁻⁹⁶, yielding intractable tars (Figure

FIGURE 26

FIGURE 27

27). The undesired 5-hydroxy chroman was treated with DDQ; again, as in the 7-hydroxy chroman case, only tars were produced.

It was found to be possible to synthesize 5-hydroxy chroman via 5-hydroxy-4-chromanol, obtained from 5-hydroxy-4-chromane upon reduction (Figure 28) with LiAlH_4 . Benzylic deoxygenation occurred upon treatment of the alcohol with Zn metal in acetic

FIGURE 28

acid. The conditions are mild, compatible with many sensitive functional groups, and yields are good. This approach is an improvement over the standard Clemmensen conditions; its general utility, however, is unknown.

Finally, the synthesis of 5-hydroxy chromene was achieved through the use of the phenacyl⁹⁷

FIGURE 29

protecting group (Figure 29). Reaction of 118 with α -bromoacetophenone in K_2CO_3 /acetone or under phase transfer conditions both failed, but the chromanol

123 did form the phenacyl ether 125 using the former conditions; the ether was formed only at the phenolic hydroxyl. Dehydration was virtually quantitative with p-toluenesulphonic acid. The phenacyl ether was cleaved under reducing conditions in high yield without any evidence of polymerization.

At this point, the feasibility of the base catalysed alkylation of 5-hydroxy-3-chromenes (Figure 4) was examined. For the reaction to occur, an anion at carbon 3 must be developed (Figure 30); thus, the proton at that position would be exchangeable in the presence of base and D_2O . However, upon incubation of 103 in D_2O in the presence of NaOD, no change in the integration of

FIGURE 30

the appropriate olefinic proton could be detected in the NMR spectrum, even after 20 hrs. Chromene 103 also proved unreactive, in a Diels Alder sense, with cyclopentadiene. This approach was then judged unsuitable for entry into the cannabinoid skeleton.

Synthesis of 5,7 dihydroxy-4-chromanones - Toward Cannabinoid Analogs

To further investigate the AB $\rightarrow$ ABC entry into cannabinoids it was decided to use the 4-chromanone system as a synthetic intermediate. As discussed in the introduction, this system has been employed by Farénholtz and co-workers¹⁷ (Figure 3), although this example suffered from poor yields. Development in this vein was undertaken.

5,7-dihydroxy-4-chromanone was synthesized according to a method by Wolfrom and co-workers⁵⁶. This process, however, is inappropriate for the synthesis of cannabinoids from olivetol, as the unnatural 7-pentyl regioisomer (80) is the major product¹⁷. In an attempt to develop the necessary methodology, an alternate route was chosen, analogous to the one used earlier (Figure 25) for the synthesis of 5-hydroxy-4-chromanone (118). Phloroglucinol was acetylated in very good yield⁹⁸ with acetonitrile in the presence of HCl and ZnCl₂. Treatment of the ketone 129 with pyrrolidine

and acetone afforded a crystalline product with a molecular weight of 261 and an NMR spectrum clearly showing the presence of the pyrrolidine system. This was not the enamine of the expected product, since the methylene protons α to the ketone were present, and the ketone itself was evident in the IR. Finally, the correct structure was determined by X-ray crystallography (Figure 32). The formation of this compound (Figure 31) may be envisaged as a Bucherer type of displacement⁹⁹ (Figure 33). Traditionally, Bucherer reactions have been shown to occur on aromatic nuclei at high temperatures and in the presence of sodium bisulphite (Figure 34). In addition, only naphthalene compounds were sufficiently reactive to undergo reactions with

FIGURE 31

FIGURE 32

FIGURE 33

FIGURE 34

secondary amines. Only the starting material 129 undergoes this reaction as 134 may be isolated in the absence of acetone, while chromanone 130 does not give the Buchener adduct, 131, under the same conditions. This may be due to the destabilization of the required keto resonance form of the phenol by strain introduced by the pyran ring.

To create a model system similar to natural cannabinoids, the hydroxyl group at the 7-position of 5,7-dihydroxy-4-chromanone was butylated with nBuBr in the presence of K_2CO_3 in acetone. Alkylation was facile and totally selective, as the C-5 hydroxyl experiences strong chelation which renders it unreactive with weak bases and weak alkylating agents. Benzyl bromide, however, was sufficiently reactive to alkylate the C-5 OH. Since the reaction conditions were the same, these two substituents could be introduced sequentially in the same pot with little or no loss of yield (Figure 35).

The Robinson annelation, under acidic conditions, of 140 was examined: In the presence of p-toluene sulphonic acid and methyl vinyl ketone, 140 afforded a 70% yield of a crystalline compound with a molecular

FIGURE 35

weight corresponding to addition of a butanone moiety. However, in the $^1\text{H-NMR}$ the C-3 methylene signal of the chromanone was intact, and only one aromatic proton remained. Aromatic substitution had occurred at either the C-6 or C-8 position (Figure 36); determination of the proper structure could not be decided on the basis of spectral data alone, due to the near symmetry of the molecule. This compound was then debenzylated with H_2 over Pd/C ; the product showed no spectral evidence of interaction between the side chain ketone and the free phenol, nor did it tend to form a hemi-ketal or enol ether under acidic conditions as might be expected for the analog substituted in the 6-position (Figure 37). Structure 145 has thus been assigned for the original alkylation product.

FIGURE 36

FIGURE 37

An approach to the alkylation of ketones, developed by Corey¹⁰⁰, involves the corresponding N,N-dimethyl hydrazone as a synthetic intermediate (Figure 38). Treatment with one equivalent of base (e.g., LDA) followed by an appropriate alkylating agent gives the substituted hydrazone in generally good yield. The parent ketone may be regenerated by treatment with cupric ion¹⁰¹. Treatment of ketone 140 with N,N-dimethyl hydrazine in the presence of an acid catalyst gave only, at best (with H_3PO_4), a 20% yield of the hydrazone derivative. Although the desired product could easily be isolated from a complex mixture of products by extraction with aqueous acid, the low yield made this route impractical.

FIGURE 38

An attempt to replicate Farenholtz's procedure¹⁷ for construction of the C-ring with substrate 140, via the hydroxymethylene derivative (149) met with failure. Upon treatment of 140 with NaH followed by ethyl formate (Figure 39), hydroxymethylene derivative, 149 was not detected; the stable enol 150 appeared to be formed instead. 150 showed no change in molecular weight from 140, and the C-3 methylene at δ 2.6 was replaced by a one proton resonance at δ 6.9 (olefinic proton) and a one proton singlet at δ 14.2 (enol proton) which was exchangeable with D₂O. Miller¹⁰², using NMR techniques, showed that for certain acenaphthene systems (Figure 40), the keto and enol forms were very close to each other in energy, but separated by a large energy barrier; the stability of the enol was increased as

the bulkiness of the ortho groups on the adjacent aromatic nucleus increased. Drieding models of 140 and 150 suggest a possible driving force, namely increased in-plane conjugation with the aromatic nucleus of the latter over the former. In addition, the pyran ring conformation in 150 puts one of the C-2 gem-dimethyls near the deshielding cone of the enol π -system. This is seen in the $^1\text{H-NMR}$ as a .43 ppm downfield shift relative to the other methyl group.

The alkylation of the enolate derived from 140 and 150 was then examined. Treatment of chromanone 140 with NaH in THF followed by quenching with

FIGURE 40

MeI afforded only enol 150, demonstrating a low nucleophilicity by both the C-3 carbon and the C-4 oxygen. Treatment of the enolate generated under the same conditions, with the more active allyl

bromide also gave no new products. However, the lithium enolate, generated by treatment with $n\text{BuLi}$, in the presence of the strongly co-ordinating solvent HMPA did afford the C-alkylated product 153 (Figure 41) in good yield along with a small amount of 154; the use of LiH as base instead of $n\text{BuLi}$ gives 153 in good yield without any trace of 154.

FIGURE 41

Suggestions for future research

Investigations into the alkylation of the aforementioned enolate continues. It is believed that the use of the appropriately functionalized allylic halides represent an important entry into the cannabinoid compounds. Two possible approaches involve the use of the Wichterle reagent¹⁰³⁻¹⁰⁶, 1,3-dichloro-2-butene or the α -halotiglates developed by Stotter¹⁰⁷ (Figure 42).

FIGURE 42

EXPERIMENTAL

Melting points were determined on a Fisher melting point block or a Mettler FP1 melting point apparatus; all melting points are expressed in degrees Celsius, and are uncorrected. ^1H -NMR spectra were obtained on Varian EM-360A or Varian T-60A 60 MHz spectrometers using CDCl_3 as solvent* and tetramethylsilane (TMS) as the internal standard; shifts are expressed in the δ scale and the following abbreviations used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infra-red (IR) spectra were obtained on a Perkin Elmer 237B grating spectrophotometer using NaCl windows as the sample support* and polystyrene film as a standard; absorbances are expressed in units of cm^{-1} . Mass spectra were determined with an A.E.I. M.S. 12 instrument at Trent University; values are expressed as m/e (relative intensity). Combustion analyses were performed by Canadian Microanalytic Laboratories at Guelph, Ontario.

Thin layer chromatographic plates were obtained from E. Merck Reagents (silica gel F-254, 0.25 mm layer thickness); preparative thick layer chromatography was performed on similar plates but with a 2mm layer

*unless otherwise noted

of silica gel. Products were detected by viewing under a UV source, or by spraying the plate with 1% ceric ammonium nitrate in 50% aqueous sulphuric acid followed by gentle heating. All ethereal reaction solvents (except for diethyl ether) were dried by refluxing over Na in the presence of benzophenone until a dark blue colour persisted, and then distilled. Anhydrous diethyl ether was purchased from Mallinckrodt and used directly. Spectral grade solvents were used for all other reactions where dryness was not critical.

The term 'rotovapped' refers to the removal of solvent in vacuo on a Buchi Rotovapor R rotoevaporator. Also, diethyl ether may be abbreviated as simply 'ether'.

Carbon-13 spectra were taken on a Bruker WP-80 spectrometer at the National Research Council, Ottawa, Ontario, or on a Varian CFT-20 at Ottawa University, Ottawa, Ontario.

Ethyl-2,6-dimethoxy-cinnamate (107) from 105

Based on a method by Mali and Yadev¹¹⁷, .70g of aldehyde 104 (4.4 mmol)⁸⁵ and phosphorane 105 (2.3g, 6.6 mmol)⁸⁶ were refluxed for one day in 15 ml of toluene under Ar. The mixture was cooled, washed with 2-10 ml portions of 2M HCl, passed through a Florisil pad, and eluted with 75 ml CH₂Cl₂. Removal of the solvent afforded .90 g (3.8 mmol) of cinnamate 107, essentially pure by TLC (86% yield). The oil solidified upon standing.

M.P. 78-80

NMR: 1.30 (t, 3H, J = 7Hz, -OCH₂CH₃); 3.85 (s, 6H, -OCH₃), 4.27 (q, 2H, J = 7Hz, -OCH₂CH₃), 6.53 (d, 2H, J = 7Hz, H-3 and H-5), 6.87 (d, 1H, J = 16 Hz, β-H), 7.25 (t, 1H, J = 7Hz, H-4), 7.80 (d, 1H, J = 16Hz, α-H)

IR: 1695 (α,β-unsaturated ester)

M.S. 236(30), 205(54), 191(64), 178(12), 177(100), 176(19), 162(18), 161(18), 149(27), 148(45), 147(17), 134(11), 133(36), 131(12), 121(16), 105(30), 103(16), 92(10), 91(73), 89(22), 85(15), 79(16), 78(19), 77(79), 76(10), 65(21), 63(33), 62(12), 53(11), 52(10), 51(85), 50(20), 45(10), 41(24)

Δ^3 -2,2-dimethyl-5-hydroxy-benzopyran (103) from 107

To 1.0 g dry Mg turnings (43.5 mmol) in 10 ml dry ether under Ar was added, dropwise, 6.7 g (46 mmol) methyl iodide in 20 ml dry ether. After refluxing for 2 h (until ~~most~~ of the Mg was consumed), 700 mg (2.9 mmol) of ester 107 in 20 ml dry ether was added dropwise, and the mixture stirred for 3 h at room temperature. Heat was again applied, and the flow of Ar increased to blow off the solvent. When the volume of the mixture reached about 5 mls, the reaction vessel was placed in an oil bath at 160° and stirring continued for 1 h. After cooling, the reaction mixture was quenched with saturated aq. NH₄Cl, and the organics extracted with ether. This solution was passed through a Florisil pad, eluted with CH₂Cl₂, the solvent removed, and the residue purified by thick layer chromatography, to give 140 mg (.79 mmol, 31%) of 103.

M.P. 125-126

NMR: 1.43 (s, 6H, C-2 gem dimethyls), 5.6 (d, 1H, J = 10 Hz, H-3), 6.23-6.53 (m, 2H, H-6 and H-8), 6.67 (d, 1H, J = 10 Hz, H-4), 6.98 (t, 1H, J = 8 Hz, H-7)

IR: (CHCl₃): 3300 cm⁻¹ (broad, phenolic OH)

M.S. 176(20), 162(14), 161(100)

2,2-dimethyl-7-hydroxy-4-keto-benzopyran (55) from 53

Resorcinol (53) (11.0 g, 100 mmol) and β,β -dimethylacrylic acid (100 g, 100 mmol) were stirred, under Ar and at room temperature, in 100 mls of POCl_3 in the presence of 50 g of ZnCl_2 ⁵⁴ for 24 h. The mixture was very carefully poured onto 2 litres of ice, with stirring, and the solids filtered and washed with water. Recrystallization from MeOH/H₂O afforded pure 55 (12.9 g, 66.8 mmol, 67%).

M.P. 165

NMR: (Acetone-d₆) 1:43 (s, 6H, C-2 gem dimethyls), 2.63 (s, 2H, H-3), 6.30-6.60 (m, 2H, H-5 and H-6), 7.67 (d, 1H, J = 8Hz, H-8), 8.73 (broad s, 1H, phenolic H)

IR: (CHCl_3) 3250 (phenolic OH), 1685 (C=O)

M.S. 192(2), 177(10), 108(18), 81(12), 80(15), 69(21), 63(15), 56(12), 55(23), 53(38), 52(79), 51(68), 50(31), 43(45), 41(100)

2,2-dimethyl-4-keto-7-tosyloxy-benzopyran (109) from 108

9.7 g (50 mmol) of chromanone 108⁵⁶, 50 g K_2CO_3 and 9.5 g p-toluene sulphonyl chloride (50 mmol) were refluxed for 3 hrs. After cooling, the mixture was filtered and the solvent removed on a rotoevaporator. The residue was recrystallized from MeOH-H₂O, affording pure crystalline 109 (14.9 g, 43 mmol, 86% yield).

M.P. 79-80

NMR: 1.42 (s, 6H, C-2 gem dimethyls), 2.43 (s, 3H, tosyl CH₃), 2.70 (s, 2H, H-3), 6.70 (broad s, 2H, H-6 and H-8), 7.35 (broad d, 2H, J = 8 Hz, tosyl Ar-H's ortho to sulphone), 7.78 (broad d, 3H, J = 8Hz, tosyl Ar-H's ortho to methyl and H-5)

IR: 1695 cm^{-1} (C=O)

M.S. 347(14), 346(56), 332(21), 331(94), 291(35), 226(10), 155(50), 107(15), 92(11), 91(100), 65(21), 63(10), 51(12)

m* 317

2,2-dimethyl-4-hydroxy-7-tosyloxy benzopyran (110) from 109

To a suspension of .41 g (10.8 mmol) of LiAlH_4 in 50 ml ether under Argon at 0°C was added, dropwise, 5.0 g of chromanone 109 (14.4 mmol) in 50 ml dry ether. After stirring for 4 hrs, the reaction was quenched with 20 ml of 20% (v/v) aqueous acetic acid.

The mixture was stirred until most of the solids had dissolved (about 1-hr), 100 ml ether added, and the mixture was filtered. The aqueous layer was removed, and the organic layer washed with 2-100 ml portions of saturated aqueous NaHCO_3 solution. Rotoevaporation followed by recrystallization from $\text{MeOH}/\text{H}_2\text{O}$ gave 3.7 g (10.8 mmol, 75%) of pure crystalline 110.

M.P. 107

NMR: 1.30 (d, 6H, $J = 7\text{Hz}$, C-2 gem dimethyls), 2.43 (s, 3H, tosyl CH_3), 4.80 (d of d, 1H, $J = 6, 8\text{ Hz}$, H-4), 6.53 (s, 1H, H-8), 6.58 (d, 1H, $J = 4\text{Hz}$, H-6), 7.36 (broad d, 3H, $J = 6\text{Hz}$, tosyl Ar-H's ortho to sulphone, H-5), 7.76 (d, 2H, $J = 8\text{Hz}$, tosyl Ar-H's ortho to methyl)

IR: (CHCl_3) 3350 (phenolic OH)

M.S. 348(36), 315(46), 293(31), 155(67), 91(100), 65(20); m^+ 245

Δ^3 -2,2-dimethyl-7-tosyloxy benzopyran (111) from 110

1.00 g (2.86 mmol) chromanol 110 and .02 g p-toluene sulphonic acid were refluxed in 50 ml toluene for 15 min. The slightly pink solution was cooled, washed with saturated NaHCO_3 solution, rotôevaporated, and recrystallized from $\text{MeOH}/\text{H}_2\text{O}$. .90 g (2.70 mmol, 94% yield) of chromene 111 was obtained as light pink crystals.

M.P. 102

NMR: 1.73 (s, 6H, C-2 gem dimethyls), 2.80 (s, 3H, tosyl Ar- CH_3), 5.63 (d, 1H, $J = 10$ Hz, H-3), 6.40 (d, 1H, $J = 10$ Hz, H-4), 6.55 (s, 1H, H-8), 6.62 (d, 1H, $J = 4$ Hz, H-6), 7.45 (broad d, 2H, $J = 6$ Hz, tosyl Ar-H's ortho to sulphone), 7.90 (broad d, 2H, $J = 6$ Hz, tosyl Ar-H's ortho to methyl)

M.S. 325(13), 316(16), 315(100), 160(20), 132(10), 91(20), 43(13)

m^* 301

2,2-dimethyl-5-hydroxy-4-keto benzopyran (118) from 117

Based on a procedure by Kabbe⁵⁹, 2,6-dihydroxy acetophenone (14.4 g, 98.6 mmol), pyrrolidine (12.2 g, 172 mmol), acetone (6.0 g, 103.5 mmol), and 100 ml of toluene were stirred for 4 days under Ar. The mixture was acidified with 100 ml of 2N HCl, the organic layer separated and washed with 3-50 ml portions of saturated aqueous NaCl, and roto-evaporated. The residue was dissolved in 50 ml CH₂Cl₂, passed through a Florisil pad, and eluted with 200 ml CH₂Cl₂. After rotoevaporation, the residue was recrystallized from Ethanol:water, to give 118 as yellow needles (14.0 g, 72.5 mmol, 74% yield).

M.P. 66

NMR: 1.47 (s, 6H, C-2, gem-dimethyls), 2.75 (s, 2H, H-3), 6.43 (d, 1H, J = 8Hz, H-6), 6.52 (d, 1H, J = 8Hz, H-8), 7.40 (t, 1H, J = 8 Hz, H-7)

IR: 3100 (broad, weak, hydrogen bonded OH)
1565 (hydrogen bonded C=O)

M.S. 192(48), 178(11), 177(100), 137(52), 136(32), 108(25), 43(15), 41(11)

2,2-dimethyl-4-keto-5-tosyloxy benzopyran(159) from 118

1.0 g chromanone 118 (5.2 mmol), p-toluenesulphonyl chloride (1.1g, 5.7 mmol), NaOH (1.0 g, 25 mmol), and TEBAC (.13g, .52 mmol) were stirred in 25 ml CH_2Cl_2 under Ar for 6 hrs. The mixture was passed through a Florisil pad, eluted with 100 ml CH_2Cl_2 , the solvent removed, and purified by column chromatography (silica gel) to give 159 as a clear oil (1.3 g, 3.7 mmol, 72% yield).

NMR: 1.33 (s, 6H, C-2 gem dimethyls), 2.40 (s, 3H, tosyl CH_3), 2.57 (s, 2H, H-3), 6.70-6.97 (m, 2H, H-6 and H-8), 7.33 (d, 2H, J = 8Hz, tosyl Ar-H's ortho to sulphone), 7.85 (d, 2H, J = 8 Hz, tosyl Ar-H's ortho to methyl)

IR: 1700 (C=O)

M.S. 346(< 1%), 91(44), 65(48), 64(20), 63(18), 56(32), 55(28), 52(20), 51(41), 50(17), 49(53), 48(20), 43(18), 41(100)

5-acetoxy-2,2-dimethyl-4-keto-benzopyran (160) from 118

0.10 g chromanone 118 (.52 mmol), powdered NaOH (.10 g, 2.5 mmol) and triethyl benzyl ammonium chloride (TEBAC) (.025 g, .12 mmol) were stirred under Ar in 5 ml dry CH_2Cl_2 . Acetyl chloride (2 ml) was added dropwise by syringe and the mixture was stirred for 20 minutes. 25 ml of CH_2Cl_2 was then added, the mixture passed through a Florisil pad, and eluted with 50 ml CH_2Cl_2 . The solvent was removed and the residue purified by thick layer chromatography to give .11 g (.47 mmol, 90% yield) of 160.

NMR: 1.43 (s, 6H, C-2 gem dimethyls), 2.33 (s, 3H, acetate CH_3), 2.63 (s, 2H, H-3), 6.60 (d, 1H, $J = 8\text{Hz}$, H-6), 6.83 (d, 1H, $J = 8\text{Hz}$, H-8), 7.43 (t, 1H, $J = 8\text{Hz}$, H-7)

IR: 1770cm^{-1} (acetate C=O), 1690cm^{-1} (C-4 C=O)

5-benzyloxy-2,2-dimethyl-4-keto-benzopyran (120) from 118

0.10 g chromanone 118 (.52 mmol), .10 g benzyl bromide (.58 mmol), and .5 g K_2CO_3 were refluxed in 20 ml acetone for 3 days. The mixture was filtered, rotovapped and taken up in 50 ml ether. After washing with 30 ml 2N NaOH followed by 30 ml H_2O , the solvent was evaporated. Recrystallization from ether/hexane gave .12 g 120 (.43 mmol, 83%) as white crystals.

M.P. 128

N.M.R. 1.45 (s, 6H, C-2 gem dimethyls), 2.70 (s, 2H, H-3), 5.20 (s, 2H, benzylic CH_2), 6.55 (d, 2H, $J = 8Hz$, H-6 and H-8), 7.20-7.73 (m, 6H, aromatic H)

IR: 1685 cm^{-1} (C=O)

M.S. 282(11), 91(100), 65(13), 41(14)

5-benzyloxy-2,2-dimethyl-4-hydroxy-benzopyran (121) from 120

1.8 g of chromanone 120 (6.3 mmol) in 10 ml of methanol was added dropwise to .34 g NaBH_4 (9.2 mmol) in 30 ml methanol. After stirring overnight under Ar, the excess NaBH_4 was destroyed by careful dropwise addition of 30 ml of 2N HCl. The resulting solution was added to 100 ml of ether and 100 ml of water in a separatory funnel, the organic layer separated and washed with a saturated sodium bicarbonate solution (2 x 50 ml). After rotoevaporation, the oily residue (1.7 g, 6.0 mmol, 95% yield) was found to be pure enough (by TLC) to proceed to the dehydration step. A small sample was purified by thick layer chromatography for analysis, confirming its identity as 121.

NMR: 1.32 (s, 3H, C-2 methyl), 1.42 (s, 3H, C-2 methyl), 2.03 (d, 2H, $J = 6\text{Hz}$, H-3), 3.37 (broad s, 1H, C-4 OH), 5.10 (t, 1H, $J = 6\text{Hz}$, H-4), 5.13 (s, 2H, benzyl CH_2), 6.57 (d, 2H, $J = 7\text{Hz}$, H-6, and H-8), 7.30 (t, 1H, $J = 7\text{Hz}$, H-7), 7.47 (s, 5H, benzyl Ar-H)

IR: 3450 cm^{-1} (benzylic OH)

Δ^3 -5-benzyloxy-2,2-dimethyl-benzopyran (122) from 121.

1.6 g (5.6 mmol) of chromanol 121 was dissolved in 50 ml of dry toluene. The solution was brought to reflux under Ar, and 50 mg of p-toluene sulphonic acid (.29 mmol) was added in one portion. After refluxing for 15 min, the solution was allowed to cool and washed with 2-10 ml portions of 2N NaOH, followed by 1-50 ml portion of distilled water. The organic layer was passed through a small Florisil pad, eluted with 100 ml CH_2Cl_2 , and rotovaporated to give 1.4 g of chromene 122 (5.2 mmol, 93%) as a slightly yellow oil, essentially pure by TLC. A small sample was purified further by thick layer chromatography.

NMR: 1.47 (s, 6H, C-2 gem dimethyls), 5.13 (s, 2H, benzyl CH_2), 5.60 (d, 1H, $J = 10$ Hz, H-3), 6.53 (d, 1H, $J = 8$ Hz, H-8), 6.51 (d, 1H, $J = 8$ Hz, H-6), 6.82 (d, 1H, $J = 10$ Hz, H-4), 7.47 (s, 5H, benzyl-Ar-H)

M.S. 266(6), 251(32), 161(12), 91(100), 65(26), 63(10), 57(14), 55(12), 51(10), 43(14), 41(200)

5-hydroxy-2,2-dimethyl-benzopyran (124) from (122)

0.10 g of chromene 122 (.37 mmol), .1 g Pd/C, and 5 ml dry ethanol were stirred under a hydrogen atmosphere. When ~ 8 ml of hydrogens were consumed, the reaction vessel was removed, and the solution filtered and rotovapped. After separation by thick layer chromatography, 43 mg of starting material was recovered along with 32 mg of 124 (.18 mmol, 86% yield based on recovered starting material).

NMR: 1.30 (s, 6H, C-2 gem dimethyls), 1.78 (t, 2H, $J = 6\text{Hz}$, H-3), 2.67 (t, 2H, $J = 6\text{Hz}$, H-4), 5.10 (broad s, 1H, phenolic O-H), 6.33 (d, 1H, $J = 8\text{Hz}$, H-6), 6.45 (d, 1H, $J = 8\text{Hz}$, H-8), 7.00 (t, 1H, $J = 8\text{Hz}$, H-7)

IR: 3350 (broad, phenolic O-H)

M.S. 178(23), 123(100), 122(11), 66(10), 55(15), 52(11), 51(12), 43(32), 41(65), 40(29)

4,5-dihydroxy-2,2-dimethyl-benzopyran (123) from 118

To a suspension of .1 g (26.3 μmol) in 50 ml anhydrous ether under Ar was added, dropwise, chromanone 118 (504 mg, 2.23 mmol) in 20 ml anhydrous ether and stirring continued overnight. After cooling to 0°C , 1 ml of water, then 1 ml of 3N NaOH, and finally 3 mls of water were added sequentially and dropwise to the reaction mixture. The solids were filtered by suction, washed with ether, and the filtrate rotovapped to give 451 mg (2.32 mmol , 88%) of 123 as a clear oil. Purification was unnecessary.

NMR: 1.27 (s, 3H, C-2 methyl), 1.37 (s, 3H, C-2 methyl), 2.03 (d, 2H, $J = 6\text{Hz}$, H-3), 3.77 (m, 1H, C-4 OH); 5.12 (t, 2H, $J = 6\text{Hz}$, H-4), 6.42 (d, 2H, $J = 8\text{Hz}$, H-6 and H-8); 7.08 (t, 1H, $J = 8\text{Hz}$, H-7)

IR: 3300 cm^{-1} (phenolic OH, benzylic OH)

2,2-dimethyl-5-hydroxy-benzopyran (124) from 123

1.0 g chromanol 123 (5.2 mmol), 2.0 g Zn dust and 20 ml acetic acid were stirred overnight. After addition of 100 ml of methanol solid NaHCO_3 was added with vigorous stirring until no further CO_2 evolution was noted. The mixture was filtered and rotovapped to afford .63 g (3.5 mmol , 67% yield) of chroman 124, essentially pure by TLC.

2,2-dimethyl-4-hydroxy-5-phenacyloxy-benzopyran (125) from

123

100 mg 123 (.51 mmol), 1 g K_2CO_3 , and phenacyl bromide (110 mg, .55 mmol) were refluxed in 20 ml acetone under Ar for 3 hrs. The orange solution was filtered, the solvent removed, and the residue purified by thick layer chromatography to give 125 (128 mg, .41 mmol, 81%) as a yellow oil.

NMR: 1.34 (s, 3H, C-2 methyl), 1.43 (s, 3H, C-2 methyl), 2.08 (d, 2H, $J = 6\text{Hz}$, H-3), 5.13 (t, 1H, $J = 6\text{Hz}$, H-4), 5.39 (5.24, benzyl CH_2), 6.41 (d, 2H, $J = 8\text{Hz}$, H-6 and H-8), 6.90 (t, 1H, $J = 8\text{Hz}$, H-7), 7.30-8.10 (m, 6H, phenacyl Ar-H)

IR: 3450 cm^{-1} (benzylic OH), 1700 cm^{-1} (phenacyl C=O)

M.S. 312(5), 279(12), 193(20), 192(53), 177(37), 141(15), 137(98), 136(23), 135(22), 134(13), 121(11), 120(11), 106(19), 105(100), 91(40), 78(13), 77(76), 65(26), 45(13), 41(24)

Δ^3 -2,2-dimethyl-5-phenacyloxy-benzopyran (126) from 125

100 mg 125 (.32 mmol) was dissolved in 10 ml toluene, and brought to reflux under Ar. p-Toluene sulphonic acid (1 mg) was added, and reflux was continued for 15 min. After allowing the solution to cool, it was washed with 20 ml of 2N NaOH, passed through a small Florisil pad, and eluted with 50 ml CH_2Cl_2 . Removal of the solvent gave chromene 126 (89 mg, .30 mmol, 93% yield), essentially pure by TLC.

NMR: 1.42 (s, 6H, C-2 gem dimethyls), 5.25 (s, 2H, phenacyl CH_2), 5.57 (d, 1H, J = 10 Hz, H-3), 6.32 (d, 1H, J = 8Hz, H-8), 6.34 (d, 1H, J = 8Hz, H-6)

IR: 1700 cm^{-1} (C=O)

M.S. 294(12), 105(48), 103(18), 91(22), 78(24), 77(100), 76(10), 65(43), 63(30), 55(21), 53(19), 52(28), 51(100), 50(54), 43(91), 41(70), 40(19)

Δ^3 -2,2-dimethyl-5-hydroxy-benzopyran (103) from 126

140 mg of 126 (.48 mmol) was dissolved in a mixture of 5 ml H₂O and 15 ml glacial acetic acid. After adding zinc dust (.13 g, 2.0 mmol) the solution was stirred under Ar overnight. The mixture was filtered, diluted with 50 ml of methanol, and neutralized with solid NaHCO₃ under vigorous stirring until no CO₂ evolution was apparent. The mixture was again filtered, and the solvent removed. Pure 103 was obtained by thick layer chromatography (62 mg, .35 mmol, 74%) as pale white flakes.

M.P. 125-126

NMR: 1.43 (s, 6H, C-2 gem dimethyls), 5.6 (d, 1H, J = 10Hz, H-3), 6.23-6.53 (m, 2H, H-6 and H-8), 6.67 (d, 1H, J = 10Hz, H-4), 6.98 (t, 1H, J = 8 Hz)

IR: (CHCl₃): 3300 cm⁻¹ (broad, phenolic OH)

M.S. 176(20), 162(14), 161(100)

2,2-dimethyl-5-hydroxy-4-keto-7-pyrrolidinyl-benzopyran
(131) from 129

A mixture of acetophenone 129 (3.1 g, 19.1 mmol)⁹⁸, pyrrolidine (3.2 ml, 2.7 g, 38.0 mmol) and acetone (1.6 g, 33.3 mmol) were heated in 75 mls of toluene until all of the solids were dissolved ($\sim 40^{\circ}\text{C}$), under Ar. Stirring was continued for 3 days, after which the reaction was cooled, acidified with 2N HCl, and the organic layer rotovapped. The residue was dissolved in CH_2Cl_2 , passed through Florisil, and eluted with CH_2Cl_2 . After removal of the solvent, the remaining material was recrystallized from MeOH/ H_2O to give 1.9 g (7.2 mmol, 38% yield) of pure 131.

M.P. 143-144

NMR: 1.45 (s, 6H, C-2 gem dimethyls), 2.00 (m, 4H, pyrrolidinyl H_3 and H_4), 2.63 (s, 2H, H-3), 3.35 (t, 4H, $J = 6\text{Hz}$, pyrrolidinyl H_2 and H_5), 5.63 (broad s, 2H, H-6 and H-8)

IR: (KBr pellet): 3450 cm^{-1} (phenolic OH) 1665 (aromatic hydrogen bonded C=O)

M.S. 262(18), 261(100), 260(18), 246(52), 206(47), 205(24), 50(10), 41(10); m^+ 232

C^{13} : 25.35 (9, C-2 gem dimethyls), 26.92 (t, pyrrolidinyl C-3 and C-4), 47.45 (t, C-3), 47.70 (9, pyrrolidinyl C-1 and C-5), 91.28 (d, C-8), 91.39 (d, C-6), 99.10 (s, C-10), 154.78 (s, C-7), 160.83 (s, C-5), 163.56 (s, C-9), 193.47 (s, C-4)

Elem. Analysis: Calc. C, 68.67; H, 7.70; N, 5.34

Found C, 68.81; H, 7.44; N, 5.38

2,6-dihydroxy-4-pyrrolidinyl-acetophenone (161) from 129

A mixture of 100 mg (.617 mmol) acetophenone 129, and 1 ml of pyrrolidine were stirred at $\sim 40^{\circ}\text{C}$ under Ar for 3 days in 10 mls of toluene. After cooling, the solvent was removed on the rotovap and the residue dissolved in CH_2Cl_2 , passed through a Florisil pad, and eluted with more CH_2Cl_2 . Purification by thick layer chromatography gave 161 as an oil (41 mg, .19 mmol, 31%).

NMR: 1.80-2.16 (m, 4H, pyrrolidinyl H-3 and H-4),
2.58 (s, 3H, COCH_3), 3.10-3.47 (m, 4H,
pyrrolidinyl H-1 and H-5), 5.67 (s, 2H, H-3
and H-5)

IR: 3300 cm^{-1} (broad, phenolic OH), 1635 cm^{-1}
(aromatic hydrogen bonded C=O)

M.S. 221(52), 220(15), 207(12), 206(100), 191(10),
70(11), 43(11); m^+ 192

5,7-dihydroxy-2,2-dimethyl-4-keto-benzopyran (130) from
128

Phloroglucinol (128) (14.8 g, 117 mmol) and β,β -dimethyl acrylic acid (12.0 g, 12.0 mmol) were stirred in 80 ml of BF_3 etherate, under Argon at room temperature, for 24 hrs.⁵⁶ The mixture was poured carefully into 1 litre of water and boiled for 10 minutes. After cooling, the yellow solids were filtered, giving essentially pure 130 (13.0 g, 62.5 mmol, 53%).

M.P. 195

NMR: (acetone- d_6): 1.40 (s, 6H, C-2 gem dimethyls), 2.68 (s, 2H, H-3), 4.30 (broad s, 2H, phenol OH), 5.85 (s, 2H, H-6 and H-8)

IR: (KBr pellet): 3150 (broad, phenolic OH) 1635 (C=O)

M.S. 209(17), 208(66), 194(12), 193(100), 176(11), 161(66), 154(66), 152(36), 149(26), 124(29), 123(12), 96(12), 91(11), 77(13); 59(36), 57(15), 56(11), 54(10), 51(15), 50(14), 43(52), 41(56)

7-butoxy-2,2-dimethyl-5-hydroxy-4-keto-benzopyran (139)
from 130

1.00 g (4.81 mmol) chromanone 130, .66 g (4.8 mmol) n-butyl bromide, and 2.5 g K_2CO_3 were refluxed in 30 ml of acetone for 12 hrs. The mixture was cooled, filtered, and rotovapped. The residue was placed on a Florisil pad and eluted with 100 ml CH_2Cl_2 . Roto-evaporation gave 1.15 g of 139 (4.35 mmol, 91%), which crystallized upon standing.

M.P. 52 -53

NMR: .92 (t, 3H, J = 7Hz, H-4), 1.45 (s, 6H, C-2 gem dimethyls), 2.67 (s, 2H, H-3), 3.98 (t, 2H, J = 6Hz, H-1), 6.00 (broad s, 2H, H-6 and H-8)

IR: 1645 cm^{-1} (hydrogen bonded C=O)

M.S. 265(16), 264(88), 250(15), 249(83), 209(43), 208(100), 189(11), 188(88), 179(11), 153(52), 152(35), 124(27), 123(20), 83(11), 69(18), 55(13), 41(24); m^+ 179, 164, 150

126.43 (d, benzy1 C-3 and C-5), 127.35 (d, benzy1 C-4), 128.48 (d, benzy1 C-2 and C-6), 136.54 (s, benzy1 C-1), 160.55 (s, C-5), 163.15 (s, C-7), 165.23 (s, C-9), 188.91 (s, C-4)

5-benzyloxy-8- (3-keto-butyl)-7-butoxy-2,2-dimethyl-4-keto-benzopyran
benzopyran (145) from 140

Chromanone 140 (4.7 g, 13.3 mmol), methyl vinyl ketone (7 ml, 6.0 g, 86 mmol), and p-toluene sulphonic acid (.4 g, 2.1 mmol) were stirred in 50 ml CH_2Cl_2 under Ar for three days. The mixture was washed with aqueous NaHCO_3 , passed through Florisil, eluted with CH_2Cl_2 , and the solvent removed. The residue was recrystallized from hexane to give 145 (4.7 g, 11.1 mmol, 83% yield)

M.P. 94.6

NMR: 1.43 (s, 6H, C-2 gem dimethyls), 2.17 (s, 3H, butanonyl COCH_3), 2.63 (s, 2H, H-3), 2.80 (t, 2H, $J=6\text{Hz}$, butanonyl CH_2CO), 4.02 (t, 2H, $J=6\text{Hz}$, H-1'), 5.23 (s, 2H, benzy1 CH_2), 5.20 (broad s, 2H, H-6 and H-8), 7.27-7.83 (m, 5H, benzy1 Ar-H)

IR: (KBr pellet): 1714 cm^{-1} (butanonyl C=O), 1675 cm^{-1} (aromatic C=O)

Elemental Analysis: Calc. C, 73.58; H, 7.55

Found C, 73.62; H, 7.57

M.S. 425(13), 424(43), 277(11), 179(11), 91(100),
43(19), 41(10)

C^{13} : 13.75 (C-4'), 17.64 (C-3'), 19.28 (butanonyl
COCH₃), 26.72 (C-2 gem dimethyls), 29.64
(butanonyl CH₂CO), 31.18 (C-2'), 43.27 (butanonyl benzylic CH₂),
50.28 (C-3), 68.08 (C-1'), 70.84 (benzyl CH₂),
78.55 (C-2), 91.09 (C-6), 105.85 (C-8), 109.89
(C-10), 126.93 (benzyl C-3 and C-5), 127.84
(benzyl C-4), 128.75 (benzyl C-2 and C-6),
137.07 (benzyl C-1), 159.60 (C-5), 159.87
(C-7), 162.91 (C-9), 190.15 (C-3), 209.19
(butanonyl C=O)

7-butoxy-2,2-dimethyl-5-hydroxy-4-keto-8-(3-keto-butyl)-
benzopyran (146) from 144

360 mg (~~0.849~~ mmol) of chromanone 144 and a small
amount of palladium charcoal (~ 20 mg) were shaken
together, in 20 ml of dry EtOH under a hydrogen atmosphere
at 1 ATM overnight. The mixture was filtered, and the
solvent removed on the rotovap, to give essentially
pure 146 (272 mg, .814 mmol, 96%).

NMR: 1.40 (s, 6H, C-2 gem dimethyls), 2.12 (s, 3H,
butanonyl COCH₃), 2.63 (s, 2H, H-3), 3.96
(t, 2H, J = 6Hz, H-1'), 5.94 (s, 2H, H-6 and
H-8)

IR: 1715 cm⁻¹ (butanonyl C=O), 1640 cm⁻¹ (aromatic C=O)

M.S. 334(.4), 69(14), 57(12), 55(17), 43(100), 41(77)

5-benzyloxy-7-butoxy-2,2-dimethyl-4-keto benzopyran

(140) from 139

To 40 ml of dry acetone was added 1.4 g of chromanone 139 (5.3 mmol), K_2CO_3 (2.0 g), and .63 ml benzyl bromide (.91 g, 5.3 mmol). The mixture was refluxed overnight under Ar, cooled, and filtered. The solvent was rotovapped off; the residue dissolved in CH_2Cl_2 , placed on a Florisil pad, and eluted with more CH_2Cl_2 . The solvent was removed, and the residue recrystallized from hexane to give 140 as white crystals (1.7 g, 4.8 mmol, 91% yield).

M.P. 82.1

NMR: 1.43 (s, 6H, C-2 gem dimethyls), 2.63 (s, 2H, H-3), 3.93 (t, 2H, $J = 6\text{Hz}$, H-1), 5.15 (s, 2H, benzyl CH_2), 6.07 (d, 1H, $J = 4\text{Hz}$, H-8), 6.10 (d, 1H, $J = 4\text{Hz}$, H-6), 7.27-7.76 (m, 5H, benzyl Ar-H)

IR: 1670 (Aromatic C=O)

M.S: 355(17), 354(65), 233(14), 91(100); m^+ 319, 251, 219, 196, 175, 147

^{13}C : 13.62 (q, C-4'), 18.99 (t, C-3'), 26.40 (q, C-2 gem dimethyls), 30.89 (t, C-2'), 50.01 (t, C-3), 67.82 (t, C-1'), 70.15 (t, benzyl CH_2), 78.58 (s, C-2), 93.99 (d, C-8), 94.54 (d, C-6), 105.34 (s, C-10)

7-butoxy-2,2-dimethyl-4-(N',N'-dimethyl-hydrazonyl)-
5-hydroxy-benzopyran (162) from 140

1.5 g of chromanone, 140 (4.25 mmol) and N,N-dimethylhydrazine (1.01 g, 16.9 mmol) were dissolved in 10 ml of dry ethanol, and stirred under Ar. A drop of conc. HCl was added, and the mixture refluxed overnight. After cooling, the solvent was removed on the rotovap and the residue dissolved in ether. The organic phase was extracted with 2N HCl; alkalization of the aqueous phase and extraction with ether followed by rotoevaporation gave an oil (which was essentially one spot by TLC); total yield of 162 was 853 mg (2.16 mmol, 51%). A small sample was purified further by thick layer chromatography.

NMR: 1.33 (s, 6H, C-2 gem dimethyls), 2.58 (s, 6H, N-methyls), 2.92 (s, 2H, H-3), 3.93 (t, 2H, $J = 6\text{Hz}$, H-1'), 5.10 (s, 2H, benzylic CH_2), 6.08 (d, 1H, $J = 2\text{Hz}$, H-6), 6.23 (d, 1H, $J = 2\text{Hz}$, H-8), 7.16-7.86 (m, 5H, benzyl Ar-H)

IR: 1670 (weak, C=N)

M.S. 396(19), 354(30), 353(10), 352(33), 306(25), 291(13), 290(21), 277(16), 275(18), 262(10), 249(11), 233(13), 206(10), 193(13), 177(10), 92(10), 91(100), 55(15), 44(12), 41(16);

Purification of the original organic phase gave 163 as an oil (132 mg, .43 mmol, 10%)

NMR: 1.40 (s, 6H, C-2 gem dimethyls), 2.55 (s, 6H, N-methyls), 2.88 (s, 2H, H-3), 3.92 (t, 2H, J = 6Hz, H-1'), 5.88 (d, 1H, J = 2Hz, H-6), 6.02 (d, 1H, J = 2Hz, H-8)

IR: 3350 cm^{-1} (phenolic OH), 1660 cm^{-1} (weak, C=N)

M.S. 307(16), 306(100), 291(29), 264(15), 250(18), 249(13), 208(22), 207(28), 206(11), 205(10), 153(13), 153(11), 69(11), 57(10), 55(14), 44(26), 43(11), 41(21); m^+ 204, 171

Δ^3 -5-benzyloxy-7-butoxy-2,2-dimethyl-4-hydroxy-benzopyran
(150) from 140

To 10 ml of dry DME under Ar was added NaH (50 mg, 2.1 mmol) followed by dropwise addition by syringe of chromanone 140 (300 mg, .848 mmol) in 5 ml dry-DME. After stirring overnight, the reaction was quenched with 2N HCl; excess water and diethyl ether were then added, the organic layer removed, and the aqueous layer extracted with another portion of ether. The combined ether portions were rotovapped and purified by thick layer chromatography, giving 150 (234 mg, .661 mmol, 78%) as a clear oil.

NMR: 1.63 (s, 3H, C-2 methyl), 2.08 (s, 3H, C-2 methyl), 4.00 (t, 2H, $J = 6\text{Hz}$, H-1'), 5.07 (s, 2H, benzylic CH_2), 6.03-6.20 (superimposed doublets, 2H, $J = 5\text{Hz}$, H-6 and H-8), 6.87 (m, 1H, H-3), 7.47 (s, 5H, benzyl Ar-H), 14.2 (s, 1H, exchangeable with D_2O , C-4 OH)

M.S. 354(5), 339(23), 91(100), 83(11); m^+ 325

^{13}C NMR 13.79 (q, C-4'), 19.17 (t, C-3'), 21.16 (q, C-2 methyl), 27.40 (q, C-2 methyl), 31.03 (t, C-2'), 67.99 (t, C-1'), 71.07 (t, benzylic CH_2), 92.20 (d, C-8), 94.47 (d, C-6), 127.21 (d, C-3), 127.94 (d, benzyl C-3 and C-5), 128.25 (d, benzyl C-4), 128.58 (d, benzyl C-2 and C-6), 135.86 (s, benzyl C-1), 151.98 (s, C-10), 161.26 (s, C-5), 165.20 (s, C-9), 167.98 (s, C-9), 187.15 (s, C-4)

5-benzyloxy-7-butoxy-2,2-dimethyl-4-keto-3-(2-propenyl)-benzopyran (153) from 140

A mixture of chromanone 140 (200 mg, .565 mmol), LiH (25 mg, 3.1 mmol), allyl bromide (.25 ml, .35 g, 2.89 mmol) and HMPA (.1 ml) were stirred under Ar in 5 ml of dry ether for three days. After quenching with 2N HCl, the ether layer was removed, rotovapped,

and the residue purified by thick layer chromatography, giving 153 (158 mg, .401 mmol).

NMR: 1.85 (s, 3H, ~~C-2~~ methyl), 2.13 (s, 3H, C-2 methyl),
3.95 (t, 2H, J = 6Hz, H-1'), 4.43-4.63 (m, 2H,
terminal methylene), 5.10 (s, 2H, benzylic CH₂),
7.43 (s, 5H, benzylic Ar-H)

IR: 1675 cm⁻¹ (C=O)

M.S. 394(12), 379(16), 91(100), 83(31), 41(15)

Attempted Synthesis of Δ^3 -2,2-dimethyl-7-hydroxy-
benzopyran (112) from 53

A mixture of resorcinol (4.3 g, 39.1 mmol) and 2,2-dimethoxy-2-methyl-2-butanol 73, (4.3 g, 34.6 mmol) were refluxed in 10 ml of pyridine, under Ar. After 24 hrs, TLC showed intact starting material and no new products.

Attempted Synthesis of Δ^3 -5,7-dihydroxy-2,2-dimethyl-
benzopyran (164) from 128

A mixture of phloroglucinol (1.26 g, 10.0 mmol) and 73 (1.48 g, 10.0 mmol) were refluxed in 10 ml of pyridine, under Ar. After 24 hrs, TLC showed that no new materials were formed.

Attempted Synthesis of Δ^3 -2,2-dimethyl-7-hydroxy-benzopyran
(112) from 113

Chroman 112 (300 mg, 1.54 mmol) and DDQ (300 mg) were refluxed under Ar, in 50 mls of dry benzene, for 2 hr. TLC revealed no isolatable products (i.e. a long streak).

Attempted Synthesis of 2,2-dimethyl-4-hydroxy-5-tosyloxy-benzopyran (165) from 118

- a) Chromanone 118 (100 mg, .288 mmol), KBH_4 (100 mg)⁹⁰, and triethylbenzyl ammonium chloride (25 mg) were stirred in a mixture of 2 mls of water and 2 mls of benzene, under Ar, overnight. TLC showed intact starting material and no new products.
- b) Chromanone 118 (500 mg, 1.44 mmol) in 20 mls dry ether was added dropwise, by syringe, to a suspension of LiAlH_4 (50 mg, 1.3 mmol) in 20 mls dry ether, and mixture stirred under Argon for 3 hrs. The reaction was quenched by addition of .50 mls water, then .50 mls 3N NaOH, and finally 1.5 mls water. The solids were filtered, washed with ether, and the combined filtrates rotovapped, to give 254 mg (1.31 mmol, 91%) of deprotected chromanol 123.

Attempted Synthesis of Δ^3 -2,2-dimethyl-7-hydroxy-benzopyran
(112) from 111

To a solution of chromene 111 (300 mg, .887 mmol) in 10 mls ethanol under Ar was added 675 mg of KOH in 5 mls EtOH. The mixture was heated to 50°C for 1 hr, cooled and taken to pH 7 with acetic acid. Addition of 100 mls of water followed by extraction with ether gave a residue which showed a long streak on TLC (no isolatable products).

Attempted Synthesis of 5-acetoxy-2,2-dimethyl-4-keto-benzopyran (166) from 118

Chromanone 118 (400 mg, 2.08 mmol) was refluxed under Ar in a mixture of 5 mls of acetic anhydride and 5 mls of pyridine, overnight. TLC showed intact material and no new materials.

Attempted Synthesis of 5-acetoxy-2,2-dimethyl-4-hydroxy-benzopyran (167) from 166

Chromanone 166 (300 mg, 1.28 mmol) in 10 mls dry dioxane was added dropwise, under Ar, to a suspension of 100 mg NaBH₄ in 10 mls dioxane. The mixture was stirred overnight, and then a small sample was quenched with 2N HCl. TLC showed intact starting material and no new products.

Attempted Synthesis of Δ^3 -2,2-dimethyl-5-hydroxy-benzopyran
(103) from 122

The debenzylation of 122 was attempted under a variety of conditions; they are listed below :

a) Chromene 122 (100 mg, .373 mmol) Pd/C (20 mg) and AlCl_3 (1 mg) were refluxed under Ar in 10 mls of cyclohexene for 24 hrs. TLC showed a long streak (no isolatable products).

b) Chromene 122 (100 mg, .373 mmol) was dissolved in 5 mls CH_2Cl_2 under Ar, and cooled to 0°C . Trichloroacetic acid (.04 ml, 65 mg, .40 mmol) was added dropwise by syringe, and the mixture stirred for $\frac{1}{2}$ hr. After quenching with 1 ml sat'd NaHCO_3 , TLC showed a long streak (no isolatable products).

c) Chromene 122 (100 mg, .373 mmol) was dissolved in 5 mls CHCl_3 under Ar, and cooled to 0°C . Trimethylsilyliodide (74 mg, .373 mmol) was added dropwise by syringe and the mixture stirred for $\frac{1}{2}$ hr. After addition of 1 ml of methanol, followed by 1 ml of H_2O , TLC showed no isolated products (i.e. long streak).

d) Chromene 122 (100 mg, .373 mmol) was dissolved in 5 ml CH_2Cl_2 , under Ar, and cooled to 0°C . BBr_3 (.04 ml, .09 g, .4 mmol) in 1 ml CH_2Cl_2 was added by syringe, dropwise, and the mixture stirred for 2 hrs. After the addition of 1 ml of MeOH followed

by 1 ml of H₂O, TLC showed no isolatable products (i.e. long streak)

e) Na-K alloy was prepared by heating sodium (76 mg, 3.3 mmol) and potassium (240 mg, 6.3 mmol) in 30 mls of xylene until melting had occurred. The molten alloy was cooled and transferred by pipette to 10 mls of 65-110° petroleum ether (10 mls) under Ar. To this was added 122 (300 mg, 1.12 mmol) in 10 mls of 65-110° pet. ether, dropwise by syringe. The mixture was refluxed for 2 hrs, and then carefully quenched with MeOH, followed by water. TLC showed no isolatable products (i.e. long streak).

Attempted Alkylations at C-3 of Chromanone 140

Chromanone 140 (150 mg, .423 mmol), LiH (50 mg, 6.3 mmol) and HMPA (.1 ml) were stirred in dry diethyl ether (15 mls), under Ar, in the presence of either MeI (500 mg, 3.31 mmol) or 4-tosyloxy-2-butanone ethylene ketal (143 mg, .500 mmol), for 24 hrs. TLC showed only the formation of enol 150.

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