CANADIAN THESES ON MICROFICHE

I.S.B.N.

THESES CANADIENNES SUR MICROFICHE

National Library of Canada
Collections Development Branch

Canadian Theses on
Microfiche Service

Ottawa, Canada
K1A 0N4

Bibliothèque nationale du Canada
Direction du développement des collections

Service des thèses canadiennes
sur microfiche

NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us a poor photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30. Please read the authorization forms which accompany this thesis.

THIS DISSERTATION
HAS BEEN MICROFILMED
EXACTLY AS RECEIVED

AVIS

La qualité de cette microfiche dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de mauvaise qualité.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, examens publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30. Veuillez prendre connaissance des formules d'autorisation qui accompagnent cette thèse.

LA THÈSE A ÉTÉ
MICROFILMÉE TELLE QUE
NOUS L'AVONS REÇUE

ML-339 (r. 82/08)

Canada

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

IN MEMORY OF MY FATHER

Then I beheld all the work of God, that a man
cannot find out the work that is done under the sun:
because though a man labour to seek it out,
yet he shall not find it; yea farther;
though a wise man think to know it,
yet shall he not be able to find it.

ECCLESIASTES 8:17

ACKNOWLEDGEMENTS

I would like to thank my research supervisor, Tony Durst, for his very personal blend of encouragement and guidance and his sensitivity in knowing when either was needed. I would also like to thank Raj Capoor for the nmr spectra and John Krause for the mass spectra. The generous supplies of podophyllotoxin, VP-16 and VM-26 and the biological test results from Bristol Laboratories, Syracuse, New York, as well as their support of this research financially were greatly appreciated. Fellowships from NSERC and the University of Ottawa are gratefully acknowledged.

I would like to express my gratitude to all my friends and family who have made the many years I've spent at university pass by quickly and enjoyably. I would like to thank my mother for her tolerance of my independent nature. I would like to thank my father for his nurturing of my quest for knowledge from an early age.

I would like to thank my heavenly Father for helping me to realize the limitations of human knowledge and for the small glimpse He has given me into the immense beauty of the universe. The desire of my heart is not to seek after the wisdom of man but the wisdom of God. "When wisdom entereth into thine heart, and knowledge is pleasant unto thy soul; Discretion shall preserve thee, understanding shall keep thee." (Prov 2:10,11)

Finally, I would like to thank Ray for leading me to the beginning of a new abundant life and a knowledge of Truth.

TABLE OF CONTENTS

LIST OF TABLES

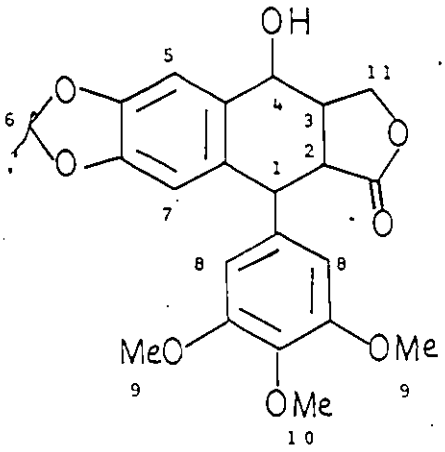
LIST OF FIGURES

LIST OF SCHEMES

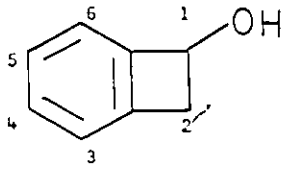
ABBREVIATIONS

n-BuLi	n-butyllithium
DCC	dicyclohexylcarbodiimide
DMF	dimethylformamide
h	hours
HMPT	hexamethylphosphoramide
HPLC	high performance liquid chromatography
IR	infrared
LDA	lithium diisopropyl amide
mp	melting point
M.S.	mass spectra
nmr	nuclear magnetic resonance
PTLC	preparative thin layer chromatography
rt	room temperature
THF	tetrahydrofuran
tlc	thin layer chromatography
TsOH	p-toluenesulfonic acid
°	refers to degrees Celsius (°C)
PCC	pyridinium chlorochromate

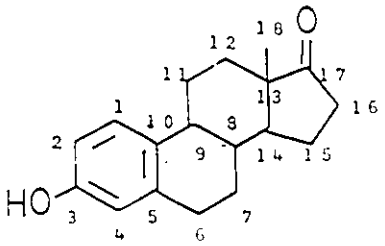
NUMBERING SYSTEMS



Podophyllotoxin analogues



Benzocyclobutenols



Estrone

ABSTRACT

In the first part of this thesis two approaches to the synthesis of podophyllotoxin analogues were reported. One involves the intramolecular cycloaddition reaction of the ortho-quinodimethane intermediate generated by thermal ring-opening of the appropriately substituted benzocyclobutenol derivative. The other involves the photoenolisation of ortho-alkyl substituted benzaldehydes and subsequent trapping of the dienol intermediate with dimethyl fumarate. The diesters, obtained in this manner, were converted by a number of different routes to the corresponding trans γ-lactones. The synthesis of (±)-epiisopodophyllotoxin by the latter route starting with 6-(3',4',5'-trimethoxybenzyl)piperonal was reported.

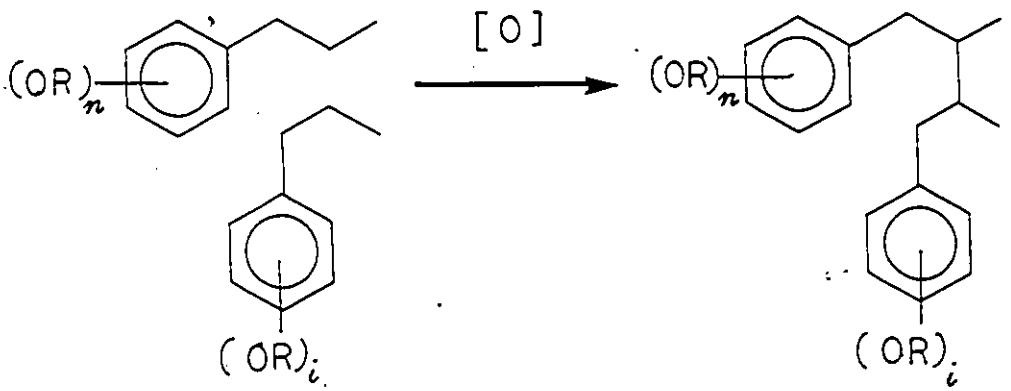
The second part of this thesis deals with the synthesis of nonenolisable podophyllotoxin derivatives. A method for substitution at C_2 in podophyllotoxin with retention of the trans lactone stereochemistry was reported along with the results of biological testing against L1210 and P388 leukemias. It was found that substitution at C_2 with a chlorine atom produced derivatives retaining the trans lactone stereochemistry that showed significant antitumour activity in the L1210 test.

But where shall wisdom be found ?
and where is the place of understanding?
Man knoweth not the price thereof;
neither is it found in the land of the living.

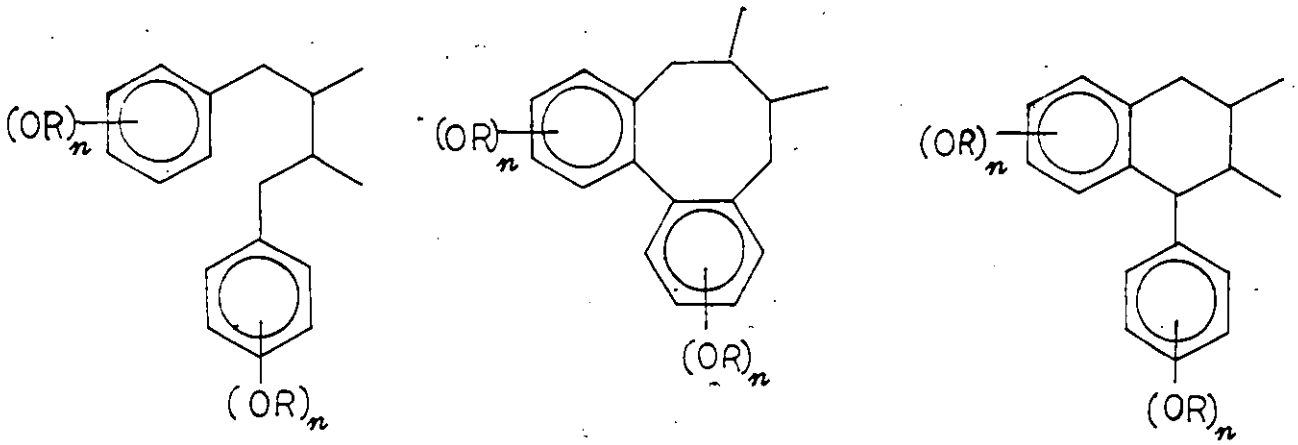
JOB 28:12,13

INTRODUCTION

The term "lignan" was used by Haworth[1] to describe the class of optically active plant products which contain the 2,3-dibenzylbutane skeleton and are probably derived by dimerization of two C_6-C_3 units at the β-carbon atoms of the two side chains.

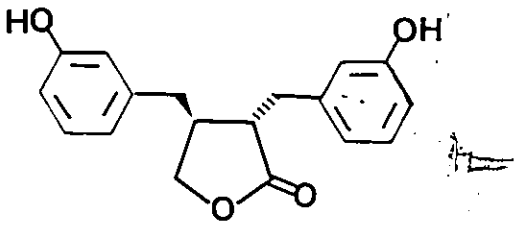


The naturally occurring skeletons can be represented by the structures of type 1, 2 and 3.

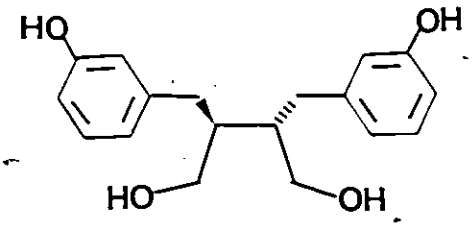


1 2 3

The term "lignan" associates this class of compounds with wood tissue. The heartwood and resin of Coniferaceae are a good source of these substances but their occurrence is not limited to this family. They have been isolated from the wood, rhizomes, seeds, oils and resins of a diversity of plant families including Lauraceae, Magnoliaceae, Piperaceae and Aralaceae. Very recently two new lignans 4 and 5 were isolated from the urine of humans, monkeys and rats.[2] Their possible biological role is not yet known.



4



5

HISTORICAL PERSPECTIVE

Podophyllum peltatum linnaeus (family: Berberidaceae ; common names: May Apple, American Mandrake, Indian Apple, Wild Lemon, Duck's Foot) is an indigenous North American, herbaceous perennial flowering in May.[3] The plant (Figure 1) was familiar to the North American Indians several hundred years ago who knew of its properties as a cathartic, anthelmintic and

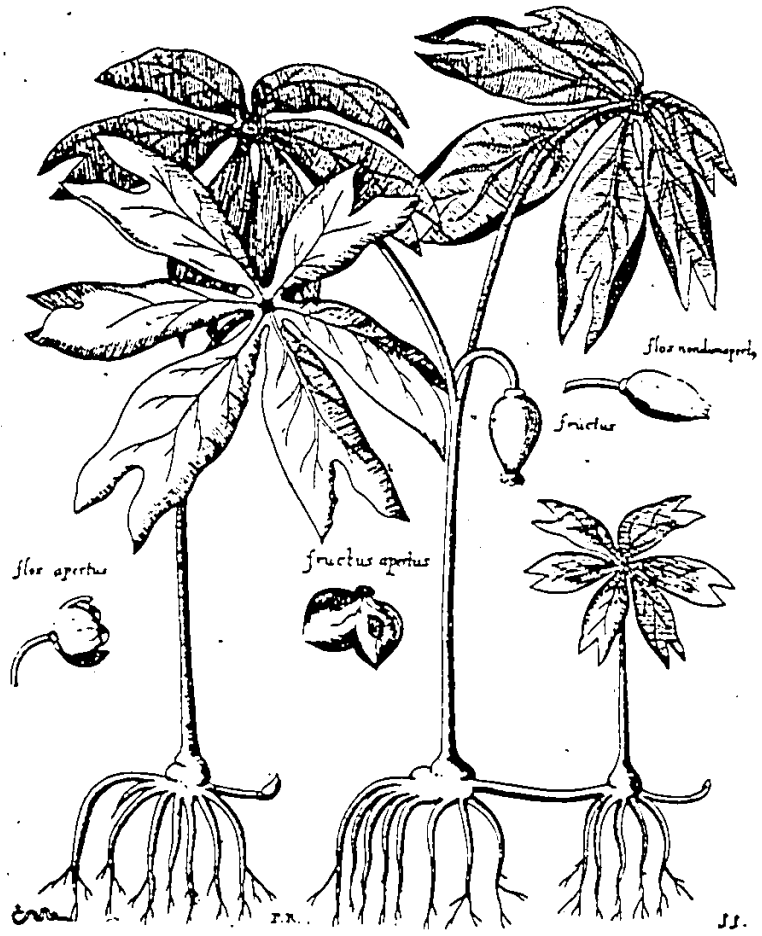


FIGURE 1 Podophyllum peltatum (May Apple)

as a poison.[4] The species of this plant growing in India, Podophyllum emodi was also used by the natives for the cathartic properties of it's root extract.

Most of the biological activity resides in the alcohol soluble portion of the root which is a complex mixture known as podophyllin or podophylum resin. Podophyllin was prepared by Dr. John King in 1835.[5] He was also the first to administer it clinically with ill effects in the initial trial described in the following excerpt of a letter to a colleague.[6]

> "...Having no idea of the intense activity of the article just discovered, I administered about twelve to fifteen grains. Nothing further was thought of the matter until about an hour afterward, when my attention was called to her condition. She was in severe pain and distress, cramps in the stomach and extremities, pulse small and feeble, extremities cold, excessive vomiting and hypercatharsis, and apparently sinking rapidly. Her condition greatly resembled that of a person suffering from a fatal attack of Asiatic cholera. To say that I was greatly alarmed would but feebly describe my mental condition. I ran to secure the aid of two or three professional friends, but could find none of them in their offices. Then I ran back again, trembling over what might be the consequences, and thinking out a course of treatment to pursue. A princely fortune could not induce me to undergo a repetition of such a condition....By perseverence in this course (of treatment), the patient recovered in six or seven days, but unfortunately, with some chronic gastroenteritic abnormal condition, that remained for many years. From this experience I was so influenced that I feared to use any of the remainder of the resin until at least eighteen months had passed, when I ventured a repetition of its use, but in much smaller quantity, and with most excellent results."

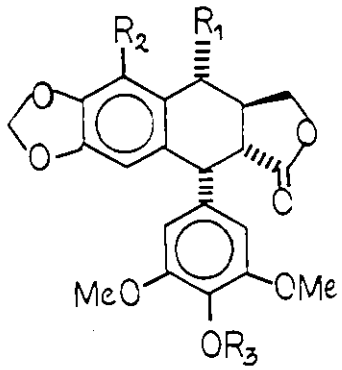
Podophyllin was included in the fourth edition of the United States Pharmacopoeia in 1863 but was dropped from the twelfth edition in 1942. The same year a report by Kaplan

appeared that suggested podophyllin was very useful in clinical treatment of a type of venereal wart (Condyloma acuminatum).[7] Between the years 1940 to 1960 podophyllin was studied in many clinical conditions including diseases of the skin due to infectious agents, non-specific dermatoses, gout, rheumatoid arthritis, benign and malignant growths.[8]

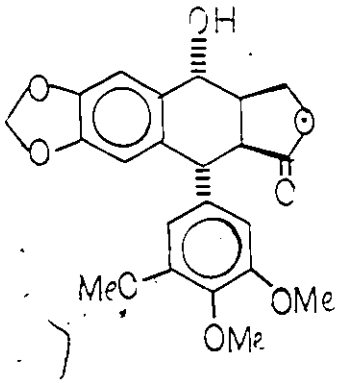
A great deal of effort by numerous investigators went into the isolation and identification of the components of podophyllin. In 1880 Podwyssotzki isolated a white crystalline substance which he named podophyllotoxin and which was believed to be the active component.[9] By 1950 seventeen compounds had been isolated and characterized ; four were flavonol pigments and the remainder were members of the lignan family.[4] The structures of the compounds isolated are shown in Table 1.

The structure and configuration of podophyllotoxin was established by chemical methods by Hartwell and Schrecker in 1958.[4] An x-ray crystal-structure analysis of 2'-bromopodophyllotoxin by Petcher in 1973[10] confirmed Hartwell's original assignment of absolute configuration as (1R,2R,3R,4R). Hartwell and Shrecker postulated that the unique antimitotic and antitumour activity of the podophyllum lignans was closely related to their unique configuration at C_1, C_2 and C_3 and the highly strained, trans-fused γ-lactone moiety. Under mild base catalysis podophyllotoxin epimerizes to picropodophyllotoxin which shows very little cytotoxic activity.[11,12]

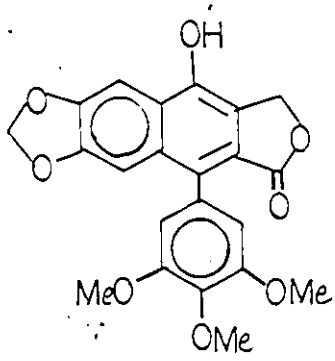
TABLE 1 : COMPOUNDS ISOLATED FROM PODOPHYLLIN



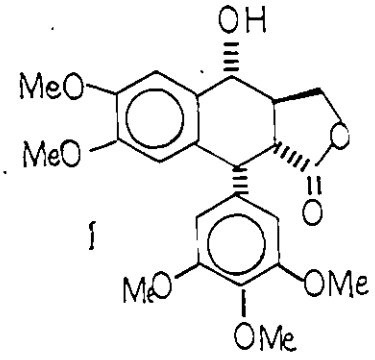
NAME	#	R_1	R_2	R_3
podophyllotoxin	6	OH	H	CH_3
α-peltatin	7	H	OH	H
β-peltatin	8	H	OH	CH_3
4'-demethylpodophyllotoxin	9	OH	H	H
deoxypodophyllotoxin	10	H	H	CH_3
podophyllotoxin glucoside	11	O-glucosyl	H	CH_3
α-peltatin glucoside	12	H	O-glucosyl	H
β-peltatin glucoside	13	H	O-glucosyl	CH_3
4'-demethylpodophyllotoxin glucoside	14	O-glucosyl	H	H



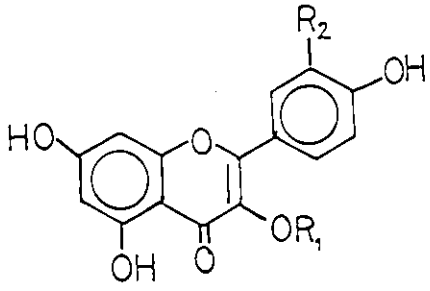
picropodophyllotoxin 15



tetradehydropodophyllotoxin 16



sikkimotoxin 17



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

A scale Dreiding model of podophyllotoxin shows a strained, inflexible molecule. On the other hand, models of picropodophyllotoxin show considerably less strain and rigidity and may exist in four interconvertible conformations.

The antimitotic activity of podophyllotoxin results from interaction with microtubules,[8,13] which are essential components of the cellular apparatus for mitosis (Appendix 1). They are hollow tube-like filaments formed by reversible polymerization of alternating α and β tubulin dimers that associate in a helical array. Assembly of microtubules from tubulin dimers can be shown in vitro to have a specific requirement for magnesium and guanosine triphosphate which are thought to be involved in stabilization of the assembled subunits (Figure 2).

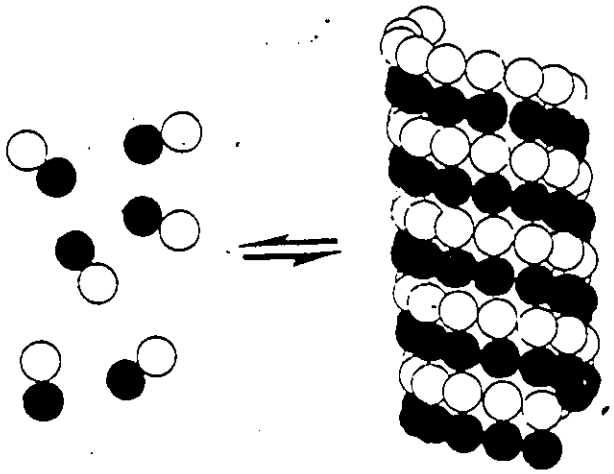
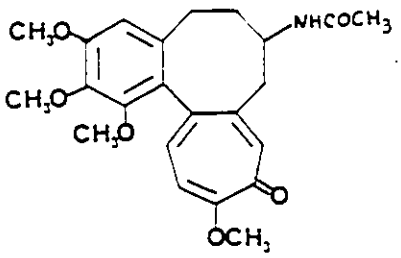


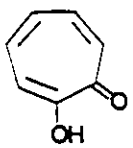
Figure 2 Assembly of tubulin dimers into microtubules

It had been known since 1955 that colchicine, 22 disrupted the assembly of microtubules, thus arresting the dividing cells in metaphase.[15] This results from noncovalent binding of col-

chicine to a high affinity ($k \simeq 2 \times 10^6 M^{-1}$) site on tubulin. It was shown that the binding site of podophyllotoxin overlaps with that of colchicine but is not identical since tropolone 23 inhibits the binding of colchicine but not podophyllotoxin. The overlapping site is thought to be where the trimethoxy-ring, common to both compounds binds.[16] Analogues with bulky substituents on the trimethoxy-ring do not bind.



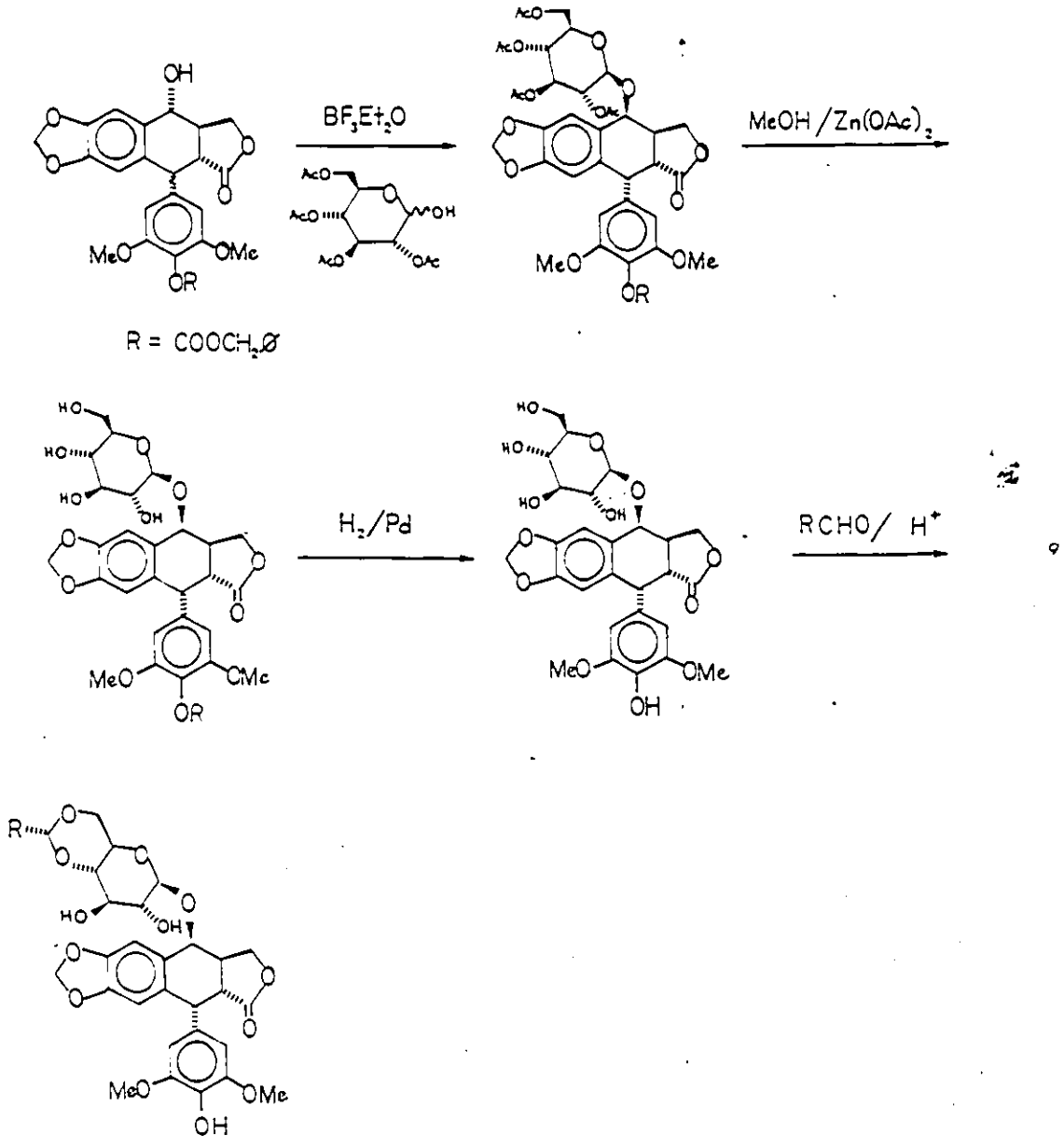
22



23

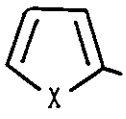
4'-Demethyl analogues of podophyllotoxin including 4'-demethylpodophyllotoxin, 4'-demethylepipodophyllotoxin, 4'-demethyldeoxypodophyllotoxin and α-peltatin induce the intracellular degradation of DNA in HeLa cells as well as affecting microtubule formation.[17]

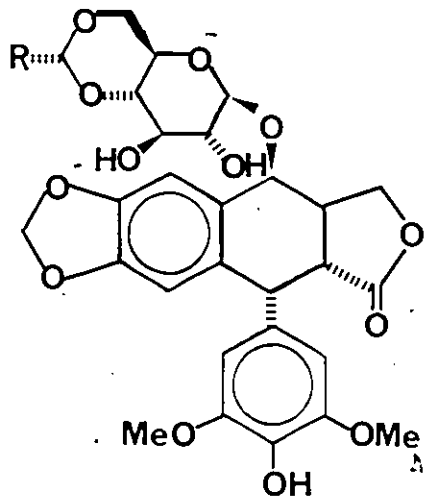
Kuhn and von Wartburg of Sandoz (Basel, Switzerland) while studying methods of preparing podophyllotoxin glycosides developed a procedure for the preparation of epipodophyllotoxin glycosides which are epimeric to podophyllotoxin at C_4.[18,19] (Scheme 1).



SCHEME 1 PREPARATION OF EPIPODOPHYLLOTOXIN GLYCOSIDES

TABLE 2 : EFFECT OF CYCLIC ACETAL DERIVATIVES ON L-1210 LEUKEMIA

R	MOUSE LEUKEMIA L-1210 % SURVIVAL TIME INCREASE
CH_3 24	167
CH_2CH_3	97
 X=S 25	121
X=O	136
C_6H_5	97
$C_6H_5CH_2$	46
1-naphthyl	95
$CH_2CH=CH$	121
$(CH_3)_3C$	57
p-FC_6H_4	64
p-$CH_3C_6H_4$	64

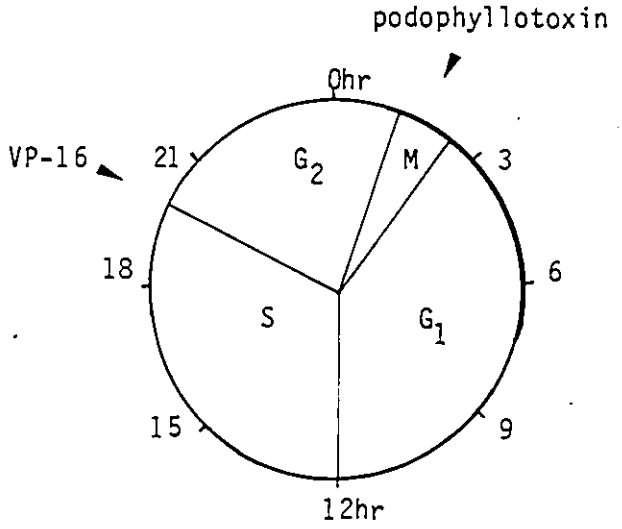


They prepared a variety of cyclic acetals of 4'-demethylepipodophyllotoxin β-glycoside and found that they exhibited not only a high activity in vitro but were much less toxic in in vivo testing against mouse lymphocytic leukemia (L-1210).[20] Two of these derivatives were selected for clinical trials and proved to be very useful in treating a variety of cancers. These were 4'-demethyl-1-O-(4,6-O-ethylidene -β-D-glucopyranosyl)-epipodophyllotoxin, 24 (VP-16 or "Etoposide"*) and 4'-demethyl-1-O-(4,6-O-(2-thenylidene)-β-D-glucopyranosyl)-epipodophyllotoxin , 25 (VM-26 or "Teniposide"*), (Table 2). These agents are active in the treatment of a wide spectrum of cancers including bladder, small cell lung, ovarian, thyroid, breast, brain, soft tissue cancers, non-lymphocytic leukemia and Hodgkin's disease.[27]

Stähelin showed that VM-26 and VP-16 prevent cells from entering mitosis and thus unlike the previously mentioned podophyllotoxin analogues they do not arrest cells in metaphase but in late S or G_2 phase of the cell cycle (Figure 3).[22] These compounds surprisingly possess a different mechanism of action other than inhibition of microtubule assembly. In fact, they have been shown not to bind to tubulin.[23] A great deal of effort has gone into determining the exact mechanism of action of these compounds but to date there is no clear answer, although the point of action appears to be the interuption of DNA transcription.[24] Very recent reports suggest that these agents interact with topoisomerase-II, an enzyme involved in the uncoiling of DNA supercoils prior to transcription.[25]

* Etoposide and Teniposide are the trade names for these compounds.

FIGURE 3: POINT OF INTERFERENCE OF PODOPHYLLOTOXIN AND VP-16 IN THE CELL CYCLE.

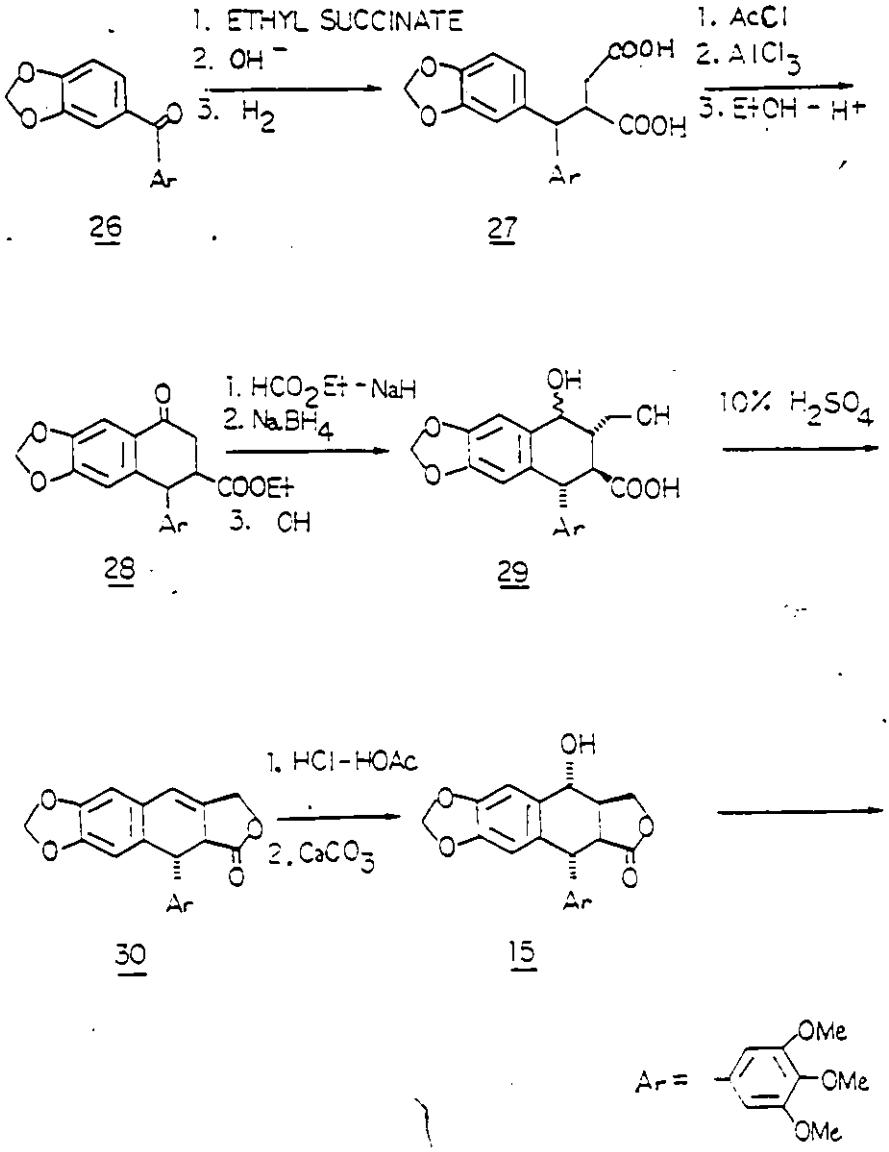


PREVIOUS SYNTHESES OF PODOPHYLLOTOXIN

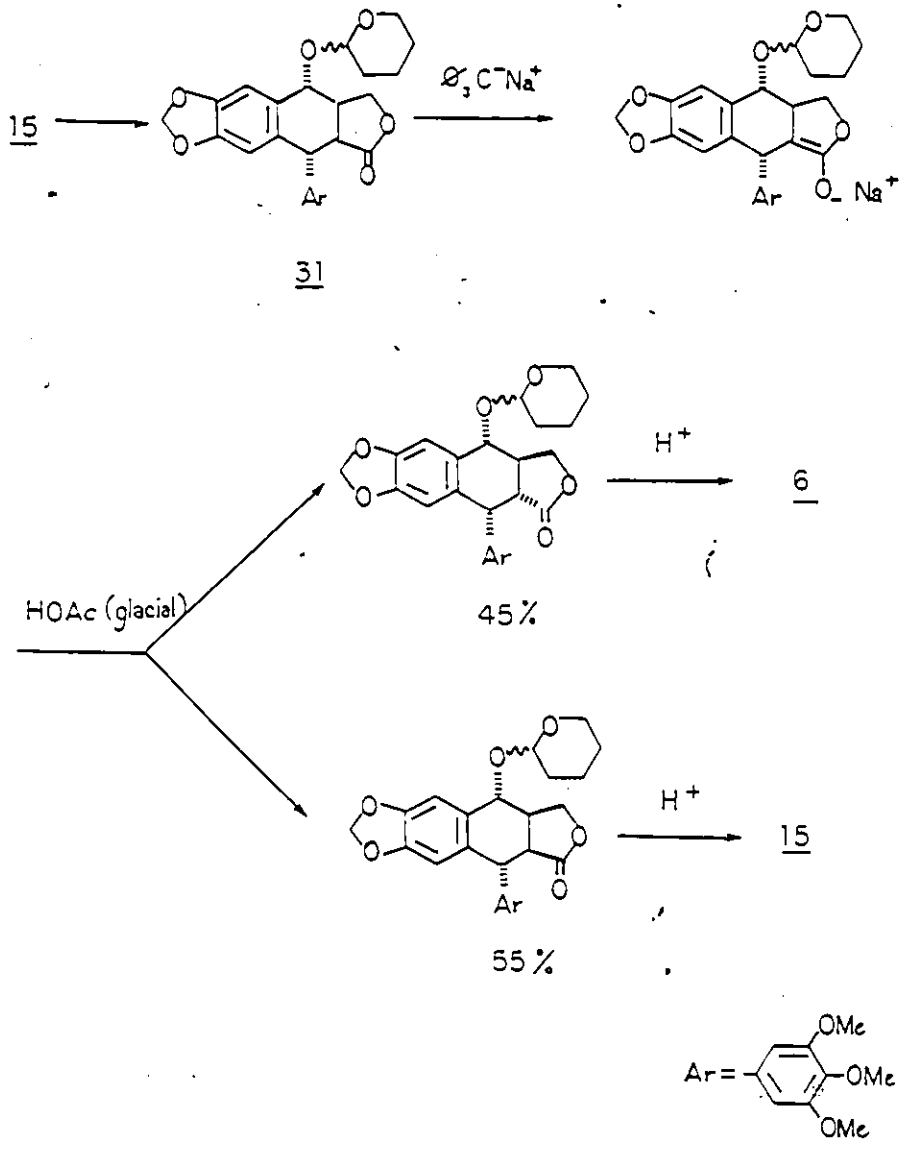
The first synthesis of podophyllotoxin 6 was reported by Gensler and coworkers in 1954 and 1966 (Scheme 2).[26] Stobbe condensation of 1-(3',4',5'-trimethoxybenzoyl)-3,4-methylenedioxybenzene 26 with ethyl succinate followed by saponification and hydrogenation gave the saturated dibasic acid 27. Conversion to the anhydride followed by intramolecular Friedel-Crafts acylation and then esterifation gave the cyclic keto-ester 28. Condensation with ethyl formate followed by sodium borohydride reduction and saponification afforded the dihydroxy acid 29. Treatment with 10% aqueous sulfuric acid gave α-apopicropodophyllotoxin 30 which was converted to picropodophyllotoxin 15 by treatment with dry HCl in glacial acetic acid followed by aqueous calcium carbonate.

Podophyllotoxin epimerizes readily under basic conditions to picropodophyllotoxin. The reverse reaction has also been demonstrated so that equilibration affords a mixture containing a 97:3 ratio of picropodophyllotoxin to podophyllotoxin.[27] Gensler avoided this thermodynamic limitation by treatment of 4-O-tetrahydropyranylpicropodophyllotoxin 31 with triphenylmethyl sodium to form the extremely rigid enolate which undergoes kinetic proton trapping with acetic acid to give a mixture of 55% picropodophyllotoxin and 45% podophyllotoxin[28] (Scheme 3).

Inspection of a model of the rigid enolate shows that there is more room for protonation above the enolate than below (Figure 4).

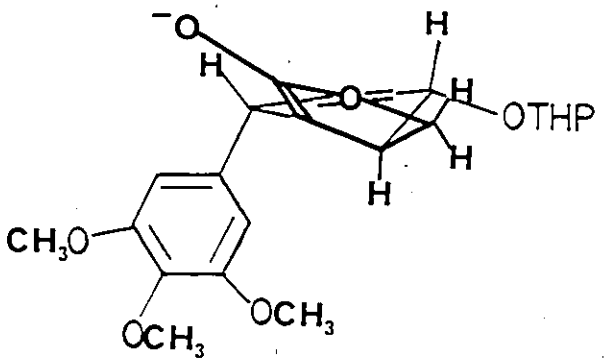


SCHEME 2 GENSLER'S SYNTHESIS OF PODOPHYLLOTOXIN (1954, 1966)

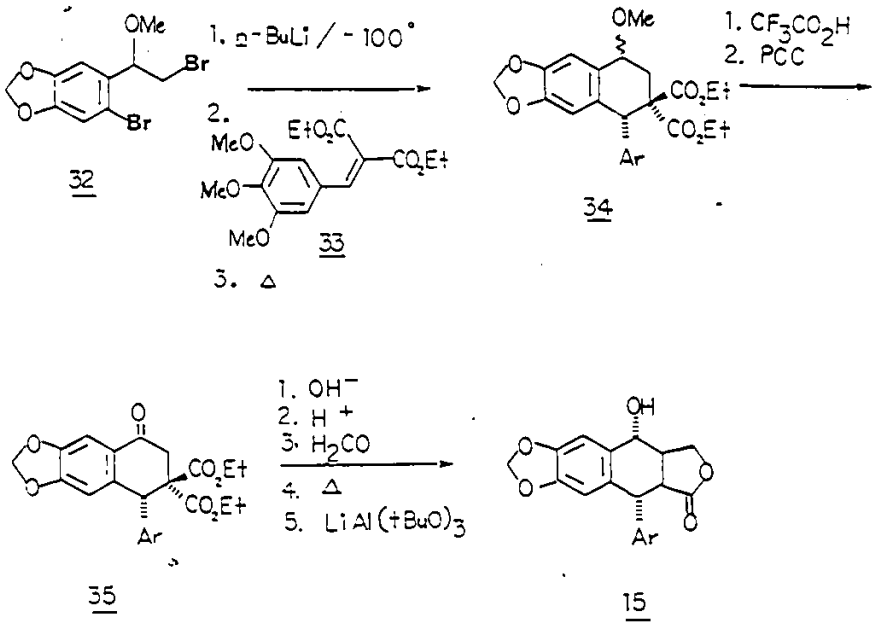

15
Ar
$\varnothing_3 C^- Na^+$
Ar
O⁻ Na⁺
31
HOAc (glacial)
H⁺
6
45%
H⁺
15
55%
Ar=
OMe
OMe
OMe

SCHEME 3

Topside protonation would afford podophyllotoxin; however, the results suggest that bottomside protonation is faster. Gensler suggested that these results may be explained if one looks at the proton transition state with the enolate carbon beginning to show sp^3 geometry. This state leads to appreciably more room below the enolate in the picropodophyllotoxin transition state. Also the change of the planar enolate transition state toward podophyllotoxin geometry introduces an unfavourable free energy factor in the activation energy due to the strain in the trans-lactone.



Kende has synthesized (±)-podophyllotoxin in 12 steps with an overall yield of 4.5% from piperonal [29,30] (Scheme 4). The methoxydibromide intermediate 32 was obtained by Wittig methylenation of piperonal followed by methoxybromination. Lithiation followed by condensation with the arylidene malonate derivative 33



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

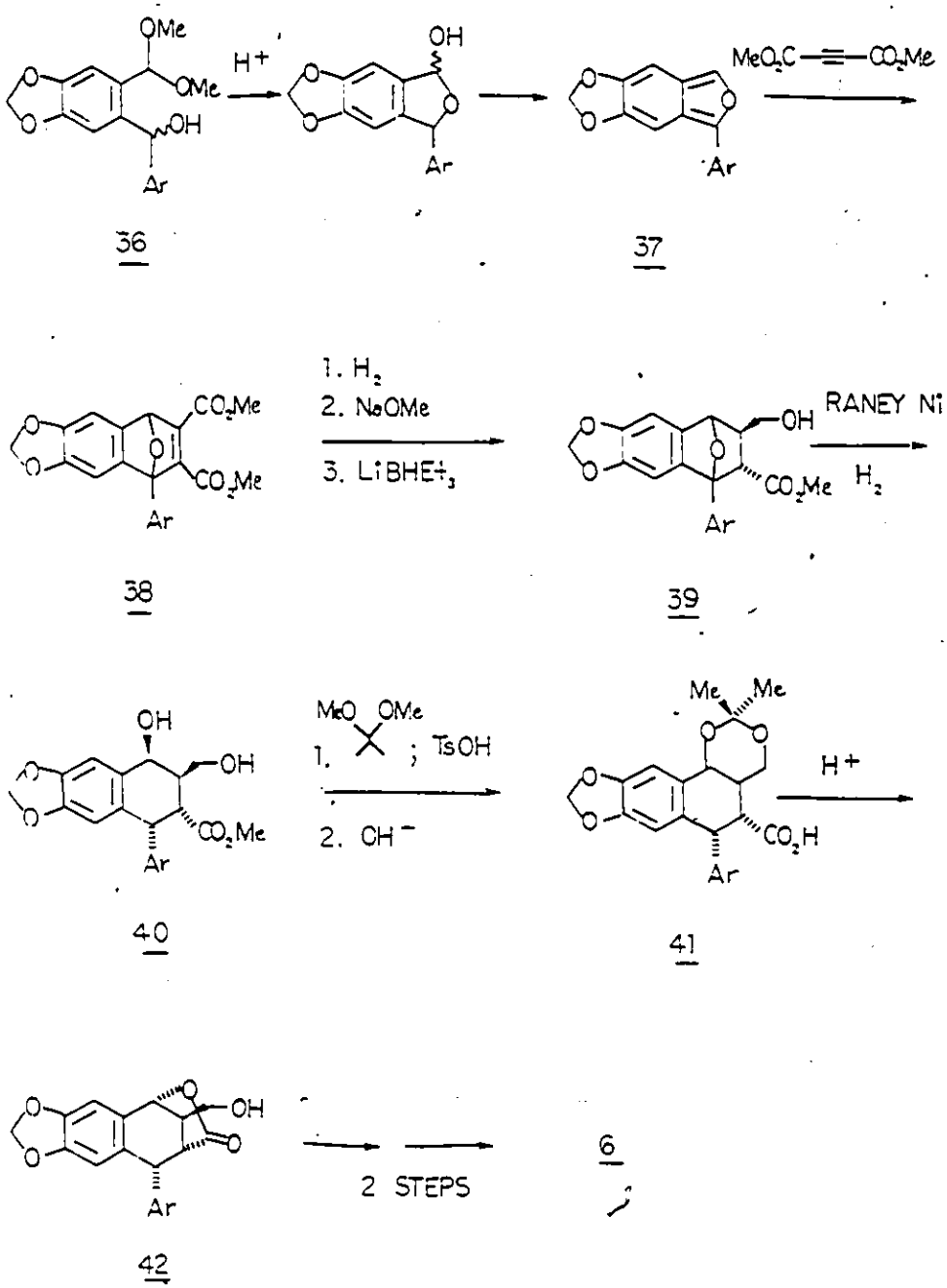
→ 6 + 15 (1:1)

SCHEME 4 KENDE'S SYNTHESIS OF PODOPHYLLOTOXIN (1981)

and subsequent heating gave the diastereomeric mixture of aryl tetralin diesters 34 in a high yield. Solvolysis followed by oxidation gave the keto diester 35 which was converted to picropodophyllotoxin 15 by the following manipulations: saponification decarboxylation, formylation, retroaldol thermolysis and finally stereoselective reduction.

In an improvement of the Gensler epimerization, picropodophyllotoxin was converted to the t-butyldimethylsilyl ether. Formation of the enolate with LDA, irreversible quenching with pyridine hydrochloride followed by desilylation afforded 36% podophyllotoxin and 34% picropodophyllotoxin.

Rodrigo's synthesis of podophyllotoxin was the first scheme devised to avoid the formidable thermodynamic hurdle present in both the Gensler and Kende syntheses[31] (Scheme 5). Lithiation of 6-bromopiperonal dimethyl acetal followed by treatment with 3,4,5-trimethoxybenzaldehyde produced the hydroxy acetal 36 which was converted to the isobenzofuran derivative 37 and trapped in situ by dimethyl acetylene dicarboxylate[32]. Catalytic hydrogenation, careful epimerization of C_3 followed by selective reduction of the C_3 ester function afforded the bicyclic hydroxy ester intermediate 39. Hydrogenation with Raney nickel gave the tetralin 40 which was converted to the acetonide 41. Saponification afforded the acid which upon treatment with dilute acid for 48 hours underwent rearrangement to (±)-neopodophyllotoxin 42.[33] This compound can be converted to (±)-podophyllotoxin 6 in two steps

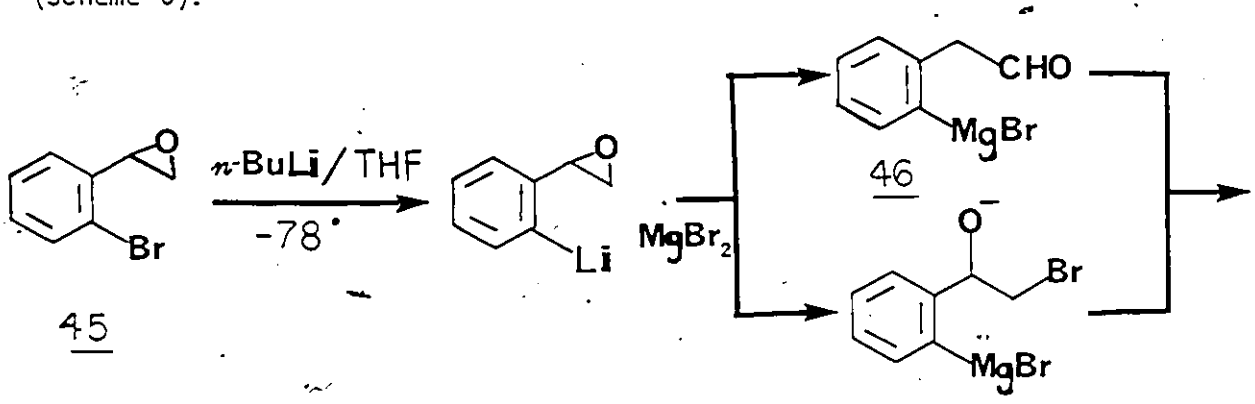


SCHEME 5 RODRIGO'S SYNTHESIS OF PODOPHYLLOTOXIN

based on the earlier work of von Wartburg and co-workers.[34] These steps consist of opening the lactone with base to give podophyllic acid and then DCC promoted lactonization.

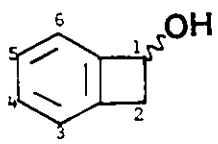
Prior to the publication of Rodrigo's synthesis of podophyllotoxin we undertook the investigation of new stereoselective routes to the synthesis of podophyllotoxin analogues and like Rodrigo we devised our scheme in order to avoid the thermodynamic hurdle of the epimerization of C_2. This could be accomplished by building in the correct stereochemical arrangement of the substituents at C_1, C_2 and C_3 early in the synthesis by a stereospecific formation of ring B.

Work in our laboratory had led to the development of a short and efficient synthesis of benzocyclobutenol 43 from ortho-bromostyrene oxide 45.[35] This interconversion involved a halogen-lithium exchange between 45 and n-butyllithium in THF at -78° to generate the lithiated epoxide, followed by either a $MgBr_2$ mediated rearrangement to the metalated phenylacetaldehyde 46 or an opening to the bromoalkoxide 47 and subsequent cyclization (Scheme 6).[36]



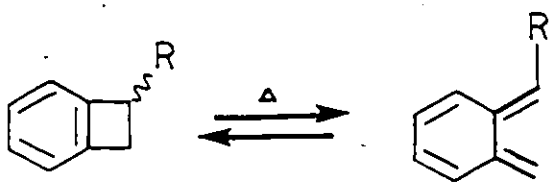
45 46 47

SCHEME 6



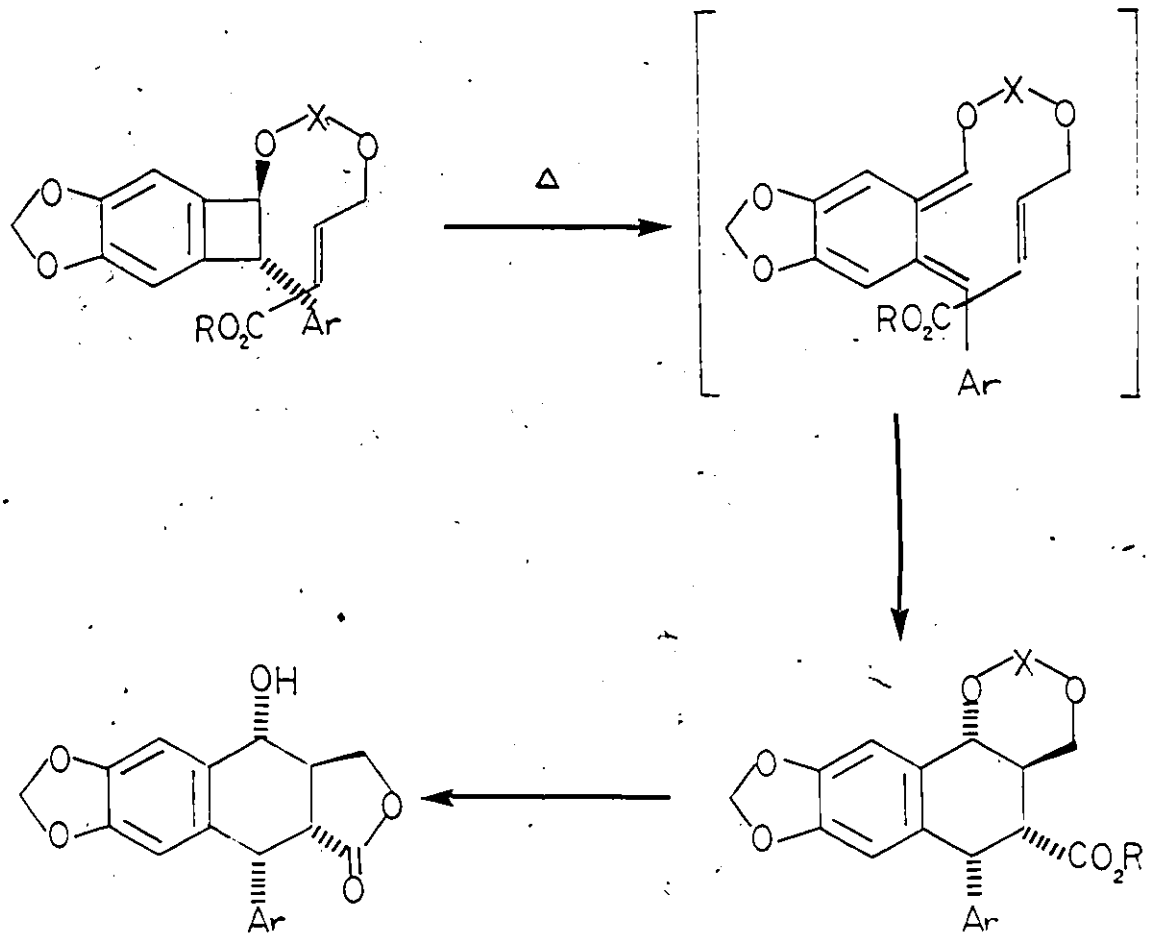
43

Benzocyclobutenes have been shown to be extremely valuable intermediates in the synthesis of natural products because of their ability to undergo reversible thermal ring opening to the reactive o-quinodimethanes 44. The latter species readily undergo both inter and intramolecular Diels-Alder reactions.[37]



44

It was our hope that the appropiately substituted benzocyclobutenol would serve as a convenient entry into the stereoselective synthesis of (±)-podophyllotoxin where the construction of ring B would occur via an intra molecular Diels-Alder reaction (Scheme 7).



SCHEME 7 PROPOSED SYNTHESIS OF PODOPHYLLOTOXIN VIA AN INTRAMOLECULAR DIELS-ALDER REACTION

But the wisdom that is from above is first pure,
then peaceable, gentle, and easy to be intreated,
full of mercy and good fruits, without partiality
and without hypocrisy. And the fruit of righteousness
is sown in peace of them that make peace.

JAMES 3:17,18

RESULTS AND DISCUSSION

PART I

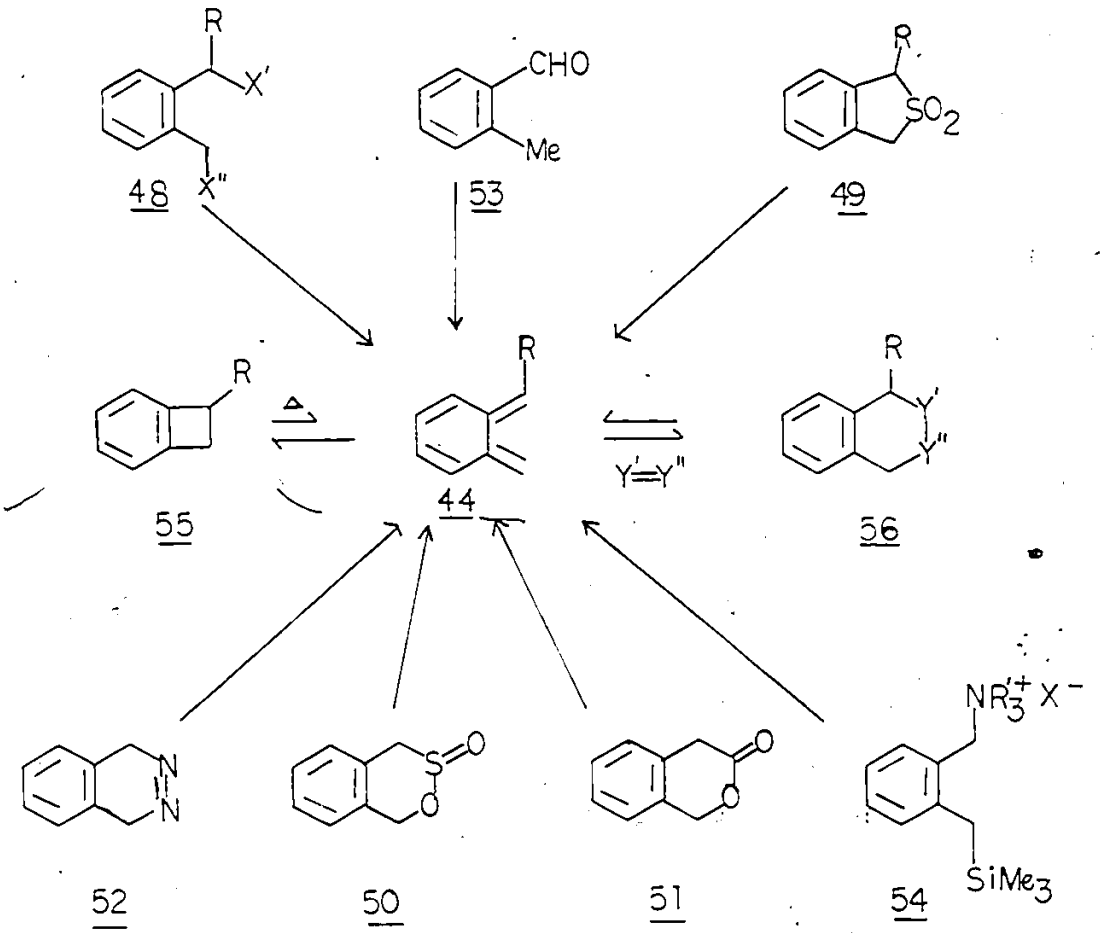
A. Intramolecular Approach to Podophyllotoxin Analogues

i. Introduction

One of the most important types of reaction used in organic synthesis is the (4+2) cycloaddition which was discovered by Diels and Alder over fifty years ago.[38] Alder recognized the possibility of intramolecular (4+2) cycloadditions in 1953[39] but this reaction was not exploited until the last decade. I would like to focus on the intramolecular (4+2) cycloadditions of a special class of dienes, the o-quinodimethanes 44.

Although it was only recently characterized by ultraviolet spectroscopy at -190°C,[41] the very reactive o-quinodimethane was recognized as early as 1957 by Cava et al. who trapped dibromo-o-quinodimethane with a variety of dienophiles.[40] Jensen also suggested the intermediacy of 44 in the thermal cycloadditions of benzocyclobutenes 55 to dienophiles giving the adducts 56.

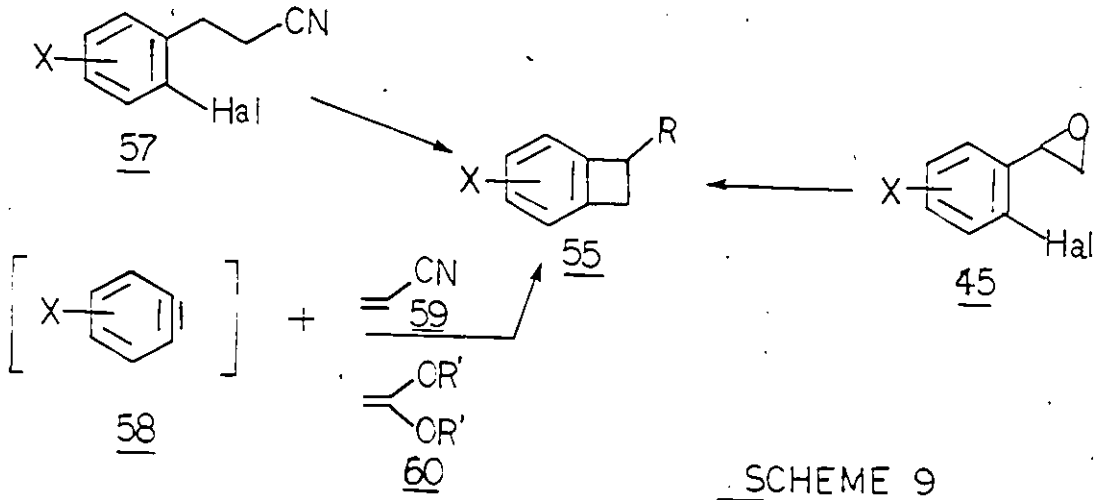
Some of the various approaches used to produce o-quinodimethanes are shown in Scheme 8. The latter species 44, formed by reductive (1,4)-elimination processes[41] (48→44), thermal or photochemical extrusion of sulfur dioxide[42] (49→44), as well as Diels-Alder cycloreversions involving the removal of sulfur dioxide from oxathiine[43] (50→44), carbon dioxide from isochromanone[44] (51→44) or nitrogen from 1,4-dihydrophthalazine[45] (52→44).


R
X'
X"
48
CHO
Me
53
R
SO2
49
R
55
44
Y'=Y"
R
Y'
Y"
56
N
N
52
S
O
O
50
O
O
51
NR'3+ X-
SiMe3
54

SCHEME 8

E-Hydroxy-o-quinodimethane 44, R=OH has been generated by photolysis of o-tolualdehyde.[46] This process involves a (1,5) hydrogen shift and will be discussed in more detail later in this chapter. More recently 44 has been generated by fluoride ion induced 1,4 elimination of o-(α-trimethylsilylalkyl)benzyltrimethylammonium halides 54.[47]

Benzocyclobutenes* 55 are a convenient source of o-quinodimethanes since they are readily accessible with a wide variety of substituents on either the aromatic or four-membered rings and they are stable under the conditions of a wide spectrum of chemical manipulations. Benzocyclobutenes have been synthesized by a number of cyclization processes (Scheme 9) such as base-induced cyclization of o-halodihydrocinnamonitriles 57[48], (2+2)-cycloadditions of benzynes 58 with olefins such as acrylonitrile 59 or ketene acetals 50[49,50] and the base induced cyclization, developed in our laboratory, of o-halostyrene oxide 45 to give benzocyclobutenol 43, R=OH.**

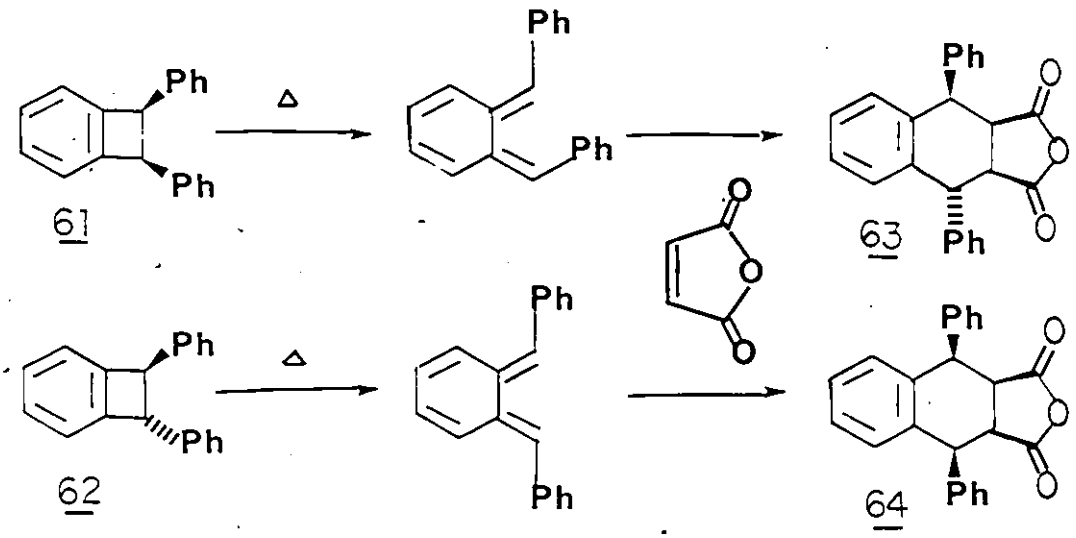


SCHEME 9

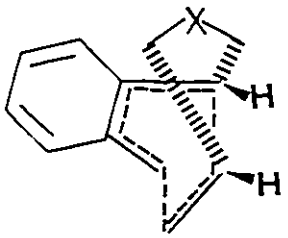
* Chemical Abstracts nomenclature is bicyclo(4·2·0)octa-1,3,5-triene.

** This reaction was discussed in the Introduction.

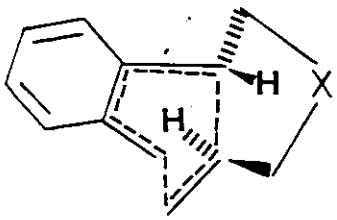
Thermal ring opening of benzocyclobutenes occurs in a conrotatory manner[51] as indicated by the stereospecific trapping of the o-quinodimethane intermediate with a dienophile via an intermolecular cycloaddition. For example, heating of the cis and trans-1,2-diphenylbenzocyclobutenes 61 and 62 in the presence of maleic anhydride afforded the tricyclic products 63 and 64 in high yields.[52]



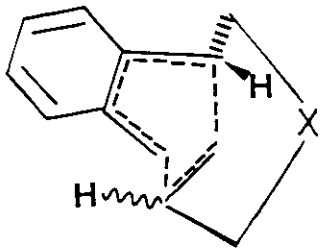
Ring opening of 1-substituted benzocyclobutenes occurs to afford the E in preference to the Z-quinodimethanes. Intramolecular (4+2)-cycloadditions to Z-o-quinodimethanes may be oriented in directions A, B or C . Furthermore, in cases where the bridge length is three or four atoms, orientation C is highly strained and may be disregarded (Scheme 10).



A endo



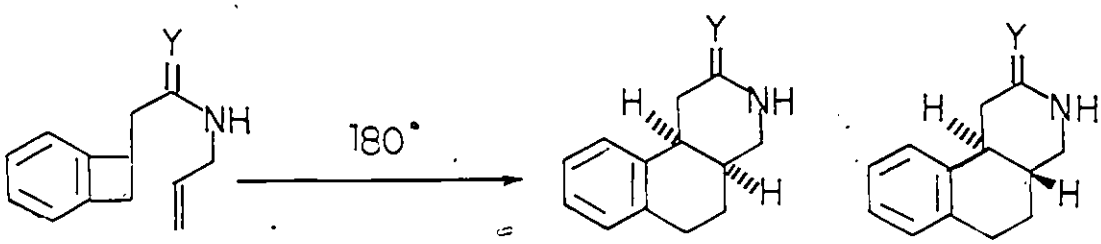
B exo



C strained

SCHEME 10 : Transition states for intramolecular (4+2) cycloadditions to Z-o-quinodimethanes where the bridge length is 3 or 4 atoms. (X=1,2 atoms)

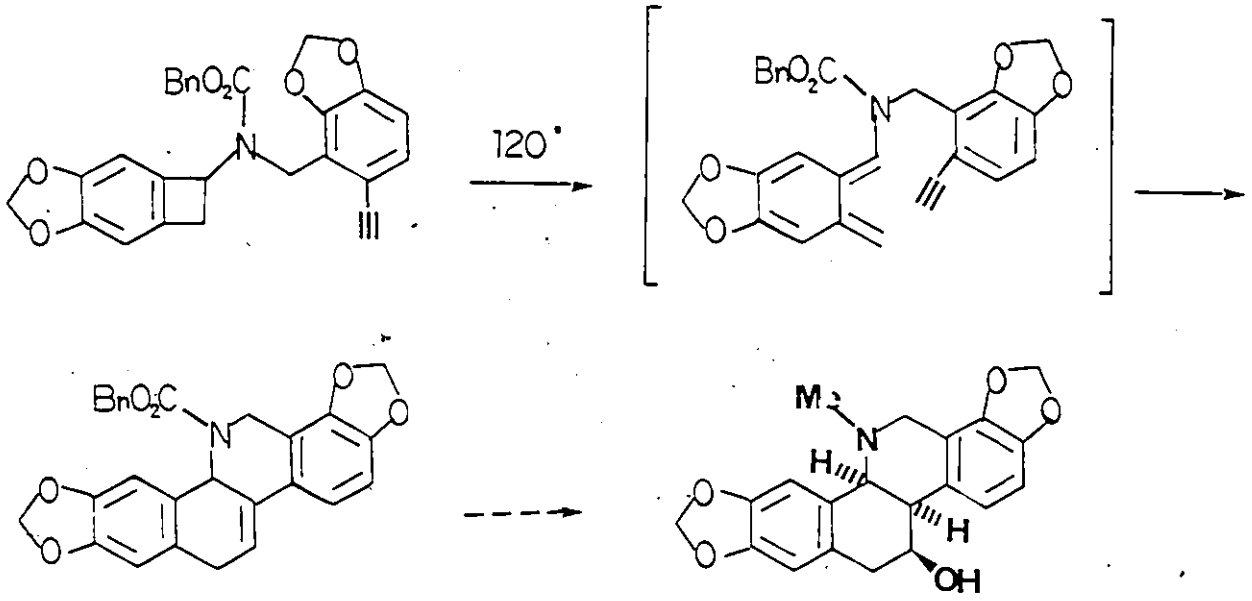
The direction of intramolecular cycloadditions towards either endo or exo products is dependent on the conformation of the bridge joining the diene and dienophile. Thus, as exeplified by the intramolecular cycloadditions of 65 and 66 , an amide moiety in the bridge alters the stereochemistry of the reaction in favour of the product resulting from an endo transition state.[53]



65	Y=H_2	67 (12%)	69 (87%)
66	Y=O	68 (79%)	70 (20%)

The preparative importance of the intramolecular Diels-Alder reaction of o-quinodimethanes can be demonstrated by studying the multitude of creative applications to the synthesis of a wide variety of natural products.

The first application of this reaction in natural product synthesis was the synthesis of (±)-chelidonine 71 by Oppolzer in 1971 (Scheme 11).[54]



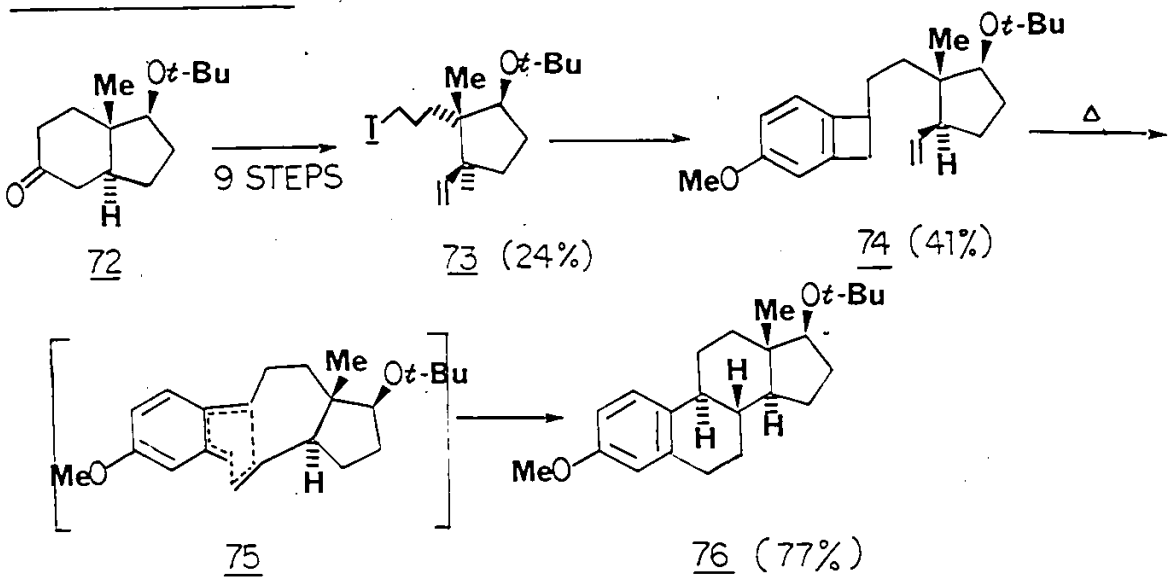
(73%)

71

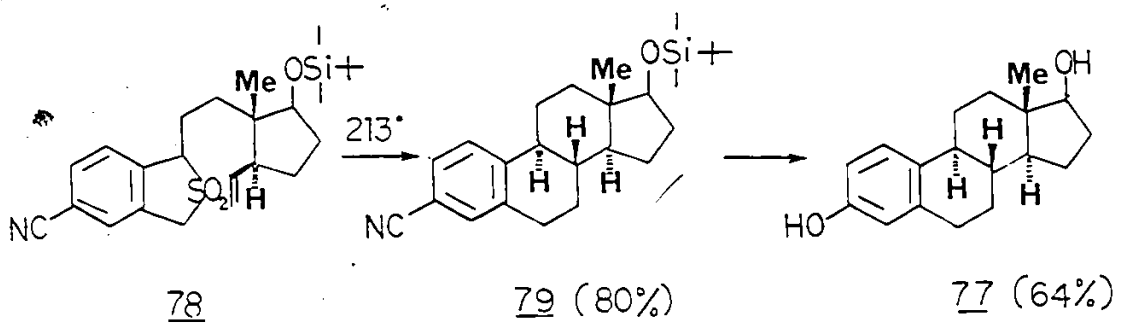
SCHEME 11

Perhaps the most popular target molecules for this reaction, for obvious reasons, have been the aromatic A-ring steroids.[55] Kametani (1978) accomplished an enantioselective approach to estradiol starting with optically pure indanone derivative 72 [56] (Scheme 12). The benzocyclobutene intermediate 74 underwent a thermal cycloaddition to afford the (+)-estradiol derivative 76 in 77% yield.

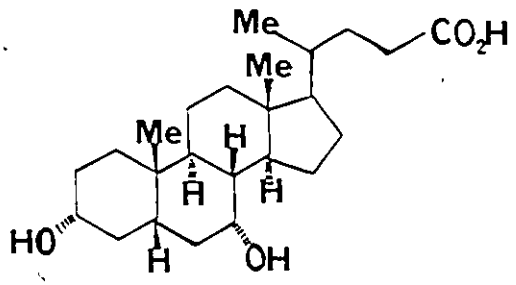
SCHEME 12



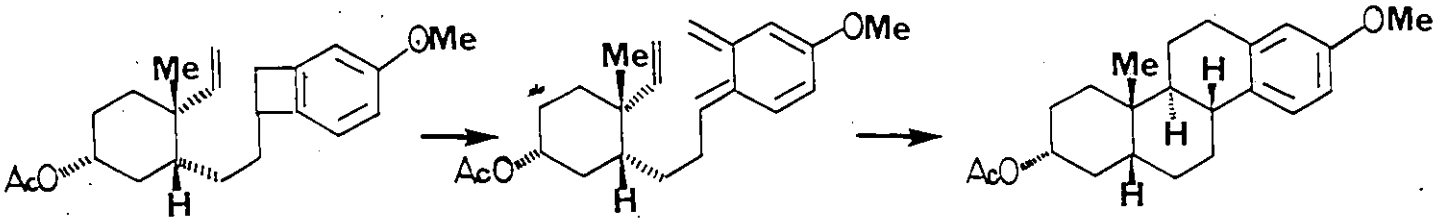
Oppolzer (1980) has also published an enantioselective synthesis of (+)-estradiol 77 starting from 1,3-dihydrobenzothiophene-2,2-dioxide, the key step being thermal sulfur dioxide extrusion of 78 and subsequent cycloaddition to give the tetracyclic intermediate 79 in 80% yield[57].



Very recently Kametani et al completed the asymmetric total synthesis of (+)-chenodeoxycholic acid 80, a compound used clinically in the treatment of gallstones.[58] The key step in this elegant synthesis was the intramolecular cycloaddition of the benzocyclobutenol intermediate 81, affording the tetracyclic adduct 82 (Scheme 13).



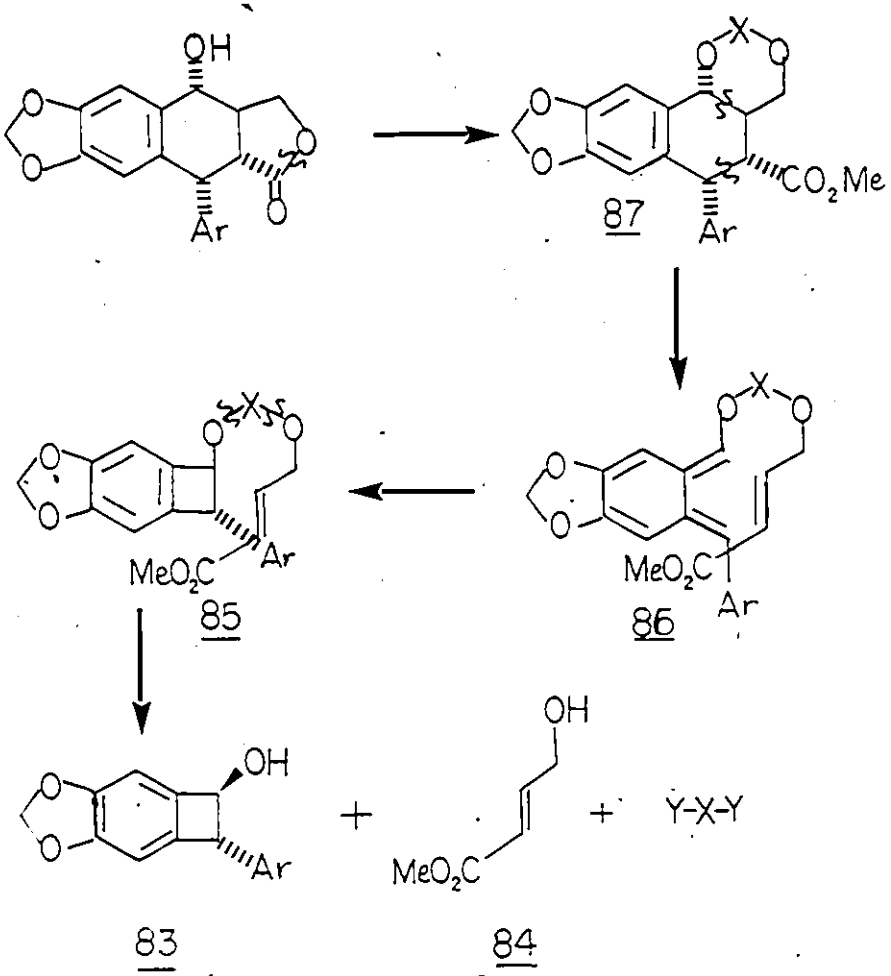
80



81 82

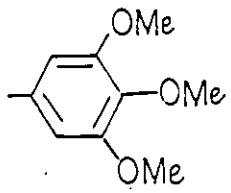
SCHEME 13

Convinced of the utility of intramolecular cycloadditions of o-quinodimethanes we decided to approach the synthesis of podophyllotoxin by this route. We believed that the hydroxyl group on the appropriately substituted benzocyclobutenol 83 would serve as a handle for directing the addition of methyl 4-hydroxycrotonate 84 to give the desired regiochemistry and stereochemistry in the cycloadditions process. Intramolecular cycloaddition of the thermally generated o-quinodimethane 86 should afford the correct relative stereochemistry of all four chiral centres in a single step. The retrosynthetic analysis is given in Scheme 14.



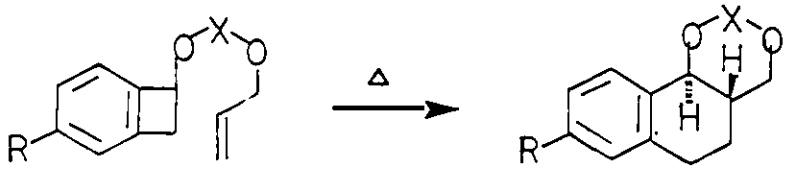
SCHEME 14

Ar =



ii. Results and Discussion

Using a model system we investigated the use of various bridging units such as -CO- , -$SiMe_2$- , and -CH_2- (Scheme 15). Although we were able to prepare the bridged compounds 88, 89 and 90 in fair yields and in a straightforward manner, only 90 (X= -CH_2-) gave the desired tricyclic adduct 91 upon thermolysis.



88 X= CO ; R=H

89 X= $SiMe_2$; R=OMe

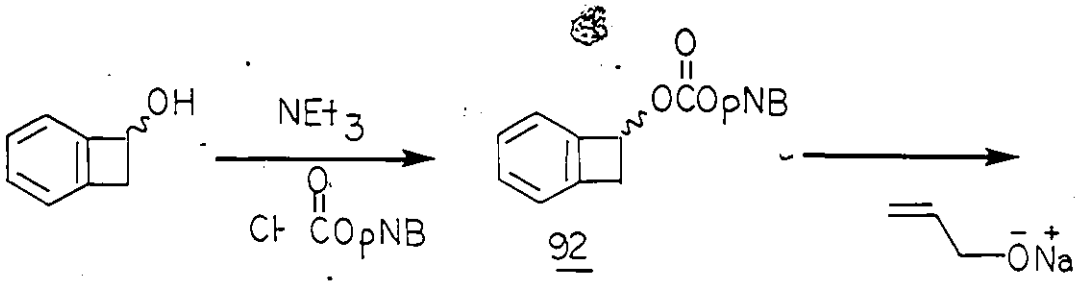
90 X= CH_2 ; R=OMe

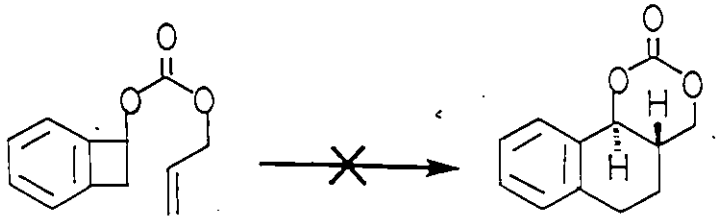
91

SCHEME 15

The carbonate, 88, was prepared in 85% yield by two consecutive displacements on p-nitrophenylchloroformate [59] ; first by benzocyclobutenol 43 and then the sodium alkoxide of allyl alcohol. Compound 88 displayed a carbonyl frequency at 1780 cm^{-1} in the infrared, characteristic of a carbonate . The ^1H nmr spectrum consisted of the expected benzocyclobutenol and p-nitrophenol

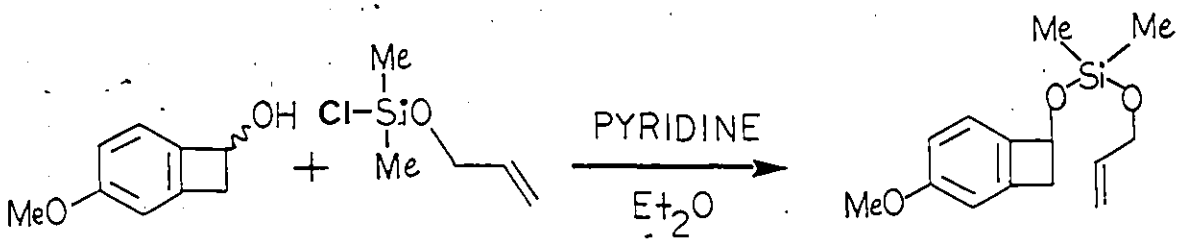
protons. The hydrogen geminal to the oxygen on the cyclobutenol portion was shifted downfield by approximately 0.8 ppm, as expected. When 88 was heated to 180° in o-dichlorobenzene no cycloaddition product was obtained. Only starting material was recovered. The inertness of 88 may be the result of the unfavourable electronic effect of the carbonate moiety on the electrocyclic ring opening process. A comparison of the rates of trapping of substituted cyclobutenes indicates the trend OMe > OH >> OAc and hence the presence of a powerful effect exerted by the substituent. Sammes reported that O-acetyl-benzocyclobutenol reacts very slowly with maleic anhydride at 180° in contrast to benzocyclobutenol which reacts rapidly at 110°.[60]





88

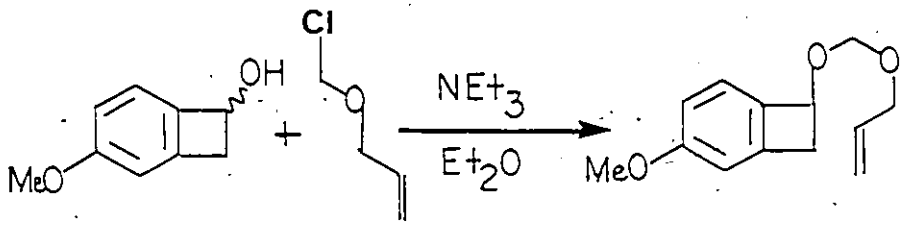
The unsymmetrical dialkoxysilane, 89, was prepared by treating 4-methoxybenzocyclobutenol 93 (see Experimental Section for the preparation of 93) with O-(chlorodimethylsilyl)-prop-1-en-3-ol 94, obtained from prop-1-en-3-ol (allyl alcohol) and dichlorodimethylsilane,[61] in the presence of pyridine. The yield for this reaction was 51%. The ^1H nmr spectrum showed a singlet at 0.10 ppm, integrating for 6H, for the $-SiMe_2-$ hydrogens, the characteristic ABX pattern for the cyclobutanol protons (H_A 2.95, H_B 3.48, H_X 5.00 ppm; J_{AB}=14.0, J_{AX}=1.5, J_{BX}=4.0 Hz) and the expected pattern for the aromatic and olefinic hydrogens. Heating of 89 at 110°, in toluene, caused extensive decomposition and resulted in the formation of none of the desired product.



93 94 89

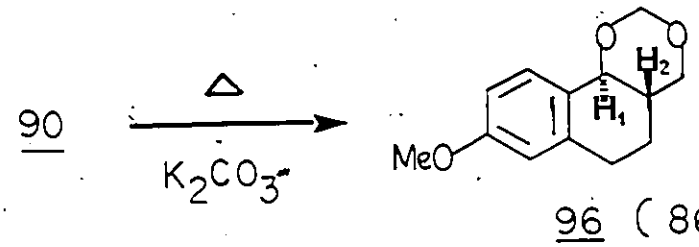
Treatment of 4-methoxybenzocyclobutenol 93 with O-chloromethyl-prop-1-en-3-ol 95, prepared from prop-1-en-3-ol by treatment with paraformaldehyde and gaseous HCl, and triethylamine in

anhydrous ether afforded 90 in 50% yield as a colorless oil after chromatography. The ^1H nmr spectrum of 90 showed, in addition to the expected 4-methoxybenzocyclobutenol and allyl hydrogens, a characteristic singlet, integrating for 2H , at δ=4.90, for the methylenedioxy protons.



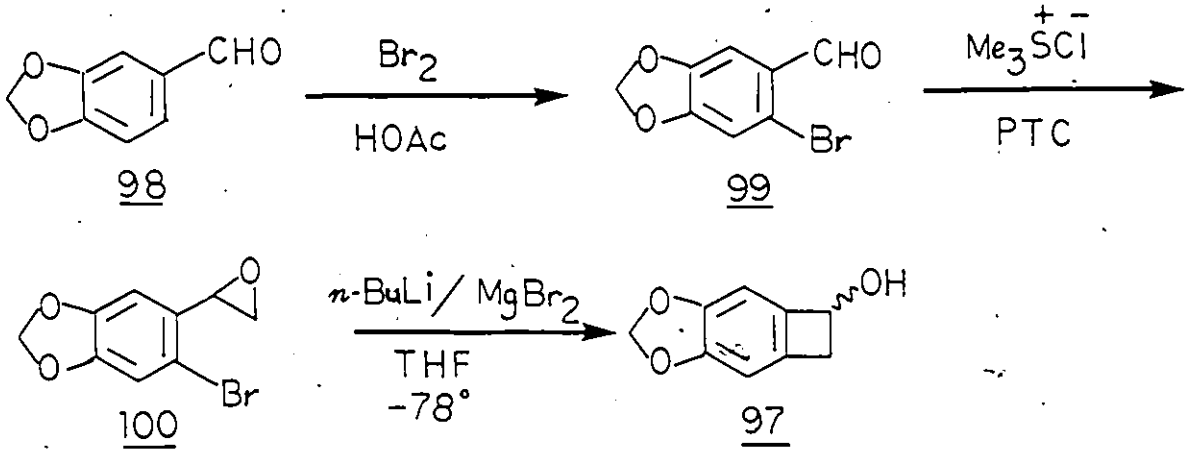
93 95 90

Heating of 90 at 110°, in toluene containing a trace of K_2CO_3, for 24h afforded the desired tricyclic cycloaddition product 96 (colorless plates, mp 76-77°) in 86% yield. The stereochemical assignment for the ring junction as trans, resulting from exo addition of the dienophile, was made on the basis of the ^1H nmr spectrum. The coupling constant, $J_{H_1-H_2}$ was found to be equal to 9.0 Hz, consistent with a diaxial relationship between these hydrogens. The inclusion of K_2CO_3, to neutralize traces of acid present in the solvent or generated during the thermolysis was found to be absolutely essential. In its absence none of the cycloaddition product was obtained.

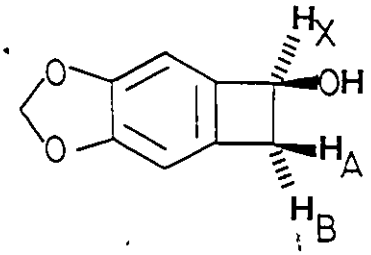


96 (86%)

This scheme was applied to the synthesis of a podophyllotoxin analogue having all the required stereochemical features but lacking a 3,4,5-trimethoxyphenyl substituent at C_1. 4,5-(Methylenedioxy)benzocyclobutenol 97 was prepared via the sequence shown in Scheme 16 starting with piperonal 98 (3,4-(methylenedioxy)benzaldehyde). Piperonal was brominated according to Orr et al. (1917)[62] using bromine in glacial acetic acid to give long colorless needles of 6-bromopiperonal 99 (mp 110°, lit. mp 111°) in 70% yield. Treatment with trimethylsulfonium chloride under phase transfer conditions afforded 6-bromo-4,5-(methylenedioxy)styrene oxide 100 (colorless prisms, mp 91°) in 82% yield. The latter was converted to the benzocyclobutenol derivative 97 using the procedure developed in our laboratory and mentioned in the Introduction. Thus, 4,5-(methylenedioxy)-benzocyclobutenol , mp 118-120°, was obtained in 75% yield. Inspection of the ^1H nmr spectrum of 97 revealed the characteristic ABX pattern for the cyclobutenol protons (Figure 4).



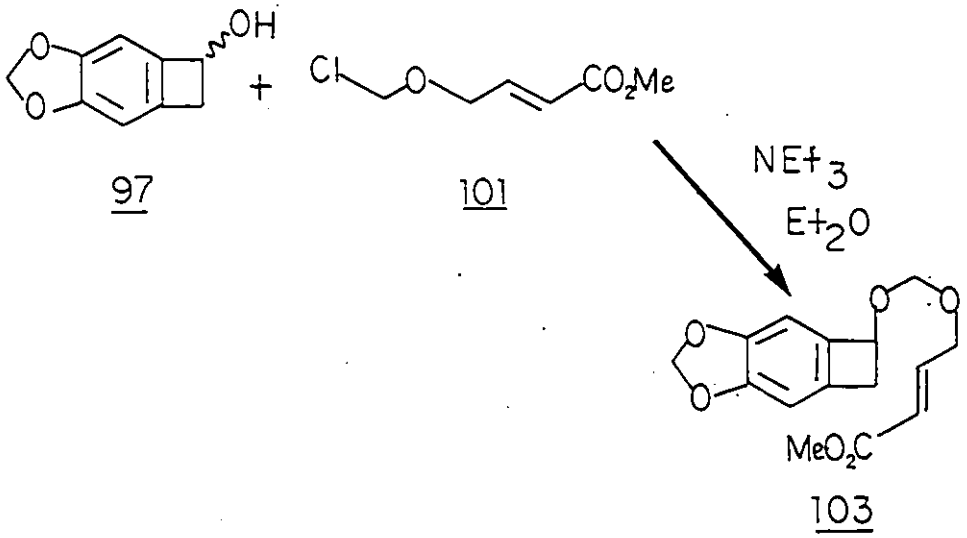
SCHEME 16



δH_X = 5.10 ppm	J_{AB} = 14.0 Hz
δH_A = 2.83 "	J_{AX} = 1.0 "
δH_B = 3.41 "	J_{BX} = 4.5 "

FIGURE 4

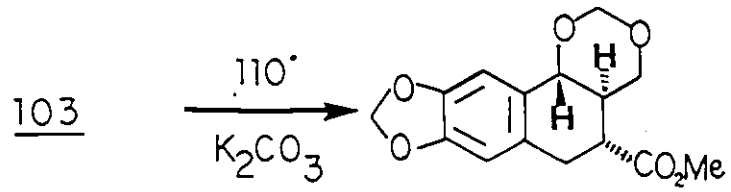
4,5-(Methylenedioxy)benzocyclobutenol 97 was coupled with methyl O-chloromethyl-4-hydroxybut-2-enoate 101, prepared from methyl 4-hydroxycrotonate 102 [63] by treatment with paraformaldehyde and gaseous HCl in CH_2Cl_2 at -20°, in the presence of triethylamine (TEA) to afford the unsymmetrical methylene acetal 103 in 60% yield. The ^1H nmr spectrum of 103 showed, in addition to the expected benzocyclobutenol and crotonate hydrogens, a characteristic singlet integrating for 2H at δ= 4.86 ppm representing the bridging methylene moiety.



97 101 103

Thermolysis of 103 in refluxing toluene containing suspended K_2CO_3 for 48h gave the desired tetracyclic adduct 104 as colorless needles (mp 155°) in 75% yield. The ^1H nmr data and suggested

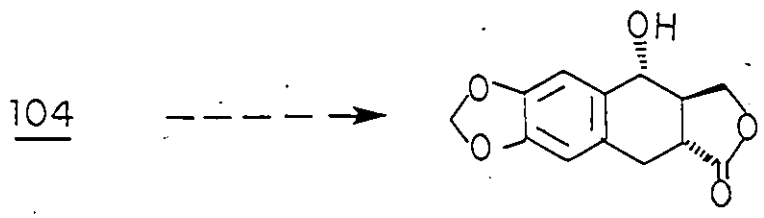
mass spectral fragmentation pathway are shown in Table 3 and Scheme 17 , respectively and are entirely consistent with the assigned structure.



104 (75%)

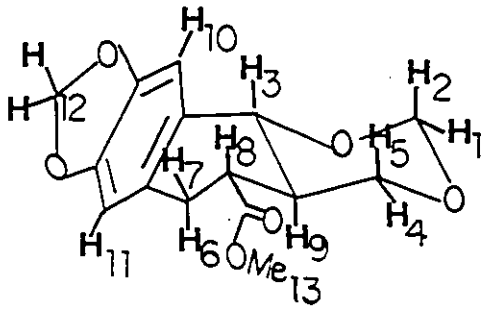
The trans relationship between H_3-H_9 and H_8-H_9 is clearly evident from the observed coupling constants; $J_{H_3-H_9}$ = 10.0 and $J_{H_8-H_9}$ = 11.6 Hz. The values of these coupling constants are consistent with pseudo-diaxial arrangements between both pairs of protons.

Compound 104 was surprisingly resistant to hydrolysis under standard aqueous acid conditions but with the proper choice of reagents should be transformable into the trans lactone derivative 105 .



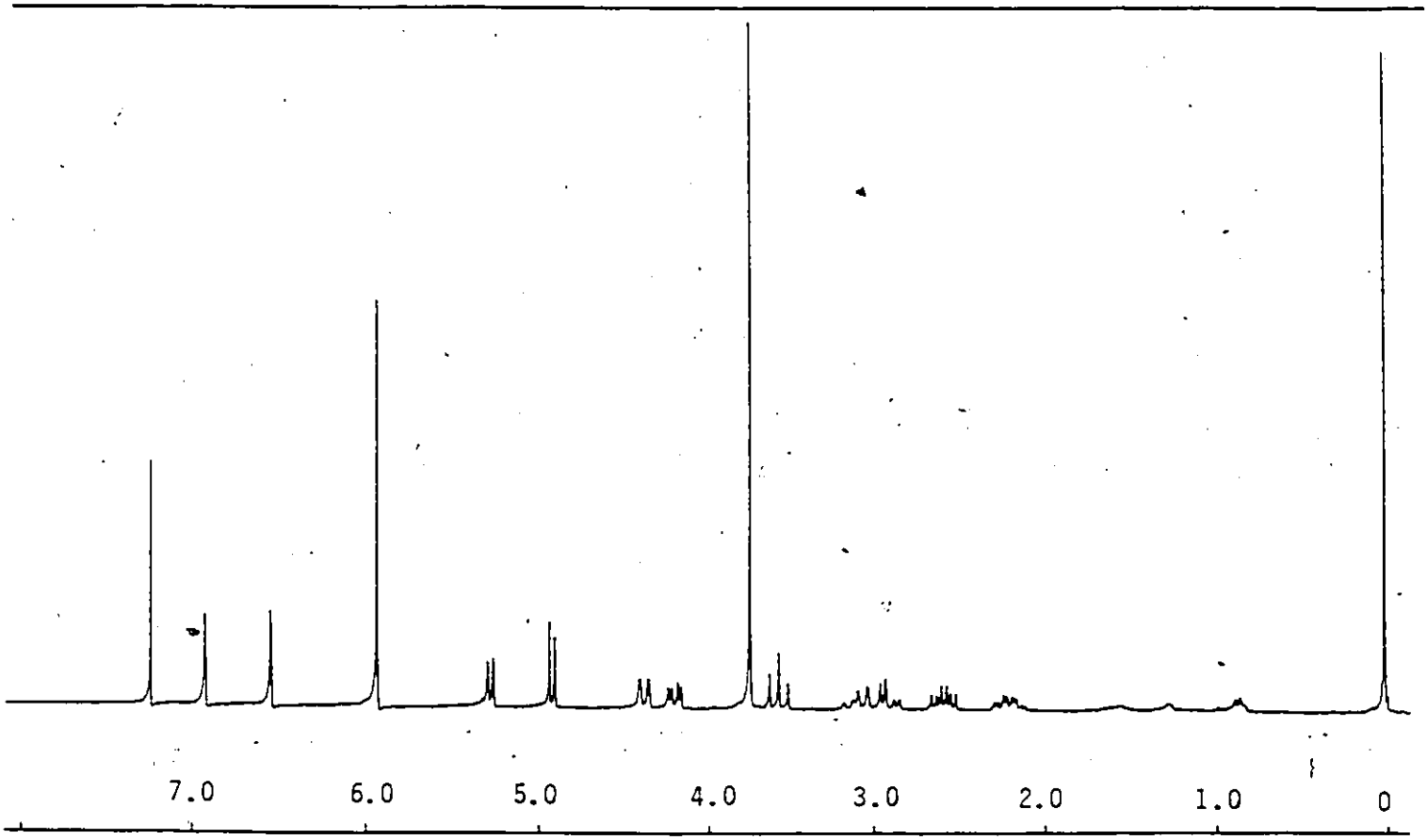
105

TABLE 3 : ^1H nmr Data for Compound 104

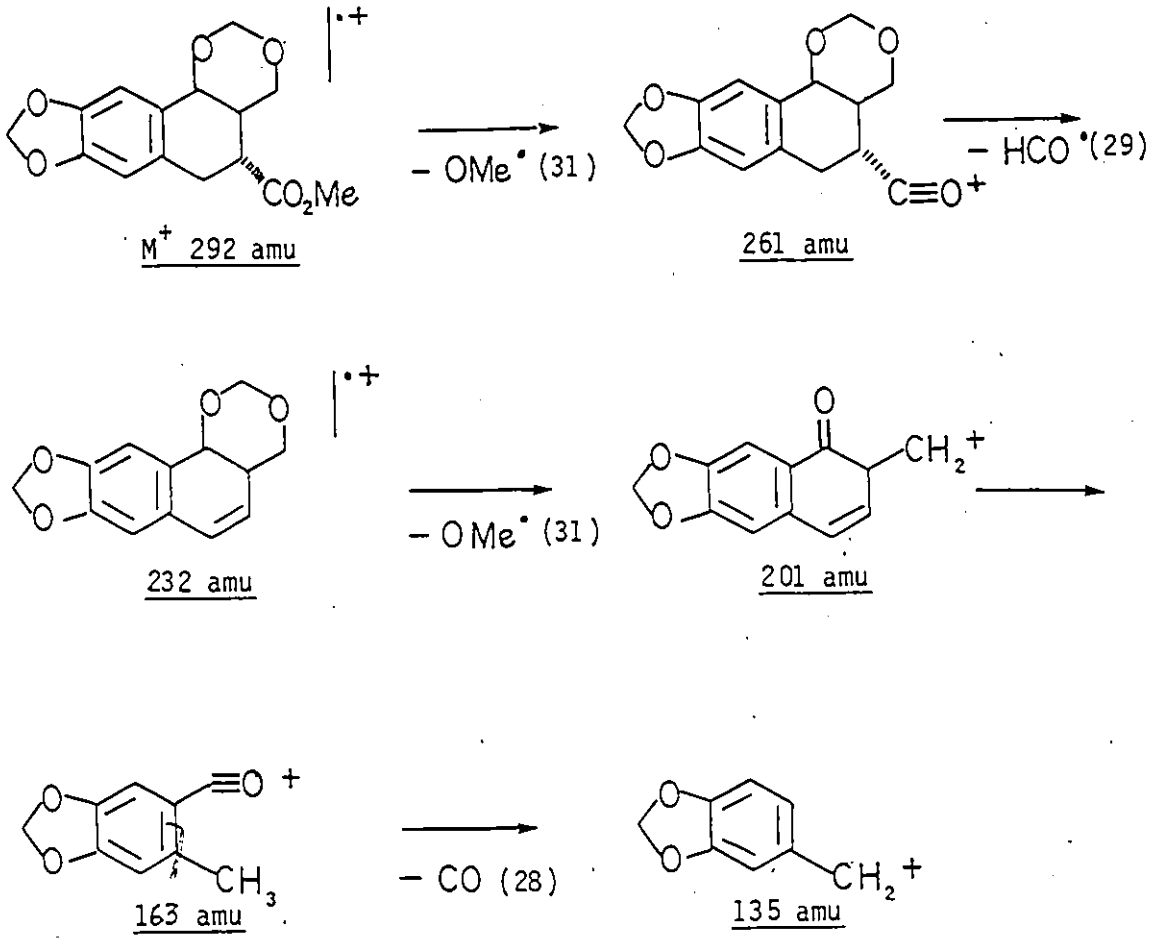


H	H_{10}	H_{11}	H_{12}	H_1	H_2	H_3	H_4	H_{13}	H_5	H_6	H_7	H_8	H_9
δ (ppm)	6.94	6.55	5.92	5.26	4.90	4.35	4.19	3.73	3.56	3.09	2.92	2.59	2.18

J_{x-y}	J_{1-2}	J_{4-5}	J_{5-9}	J_{9-4}	J_{7-6}	J_{8-6}	J_{3-9}	J_{8-9}	J_{7-8}	$J_{12-12'}$
Hz	6.2	11.0	11.0	4.0	11.6	10.4	10.0	11.6	6.1	<0.5



SCHEME 17 Proposed Mass Spectral Fragmentation Pathway of 104

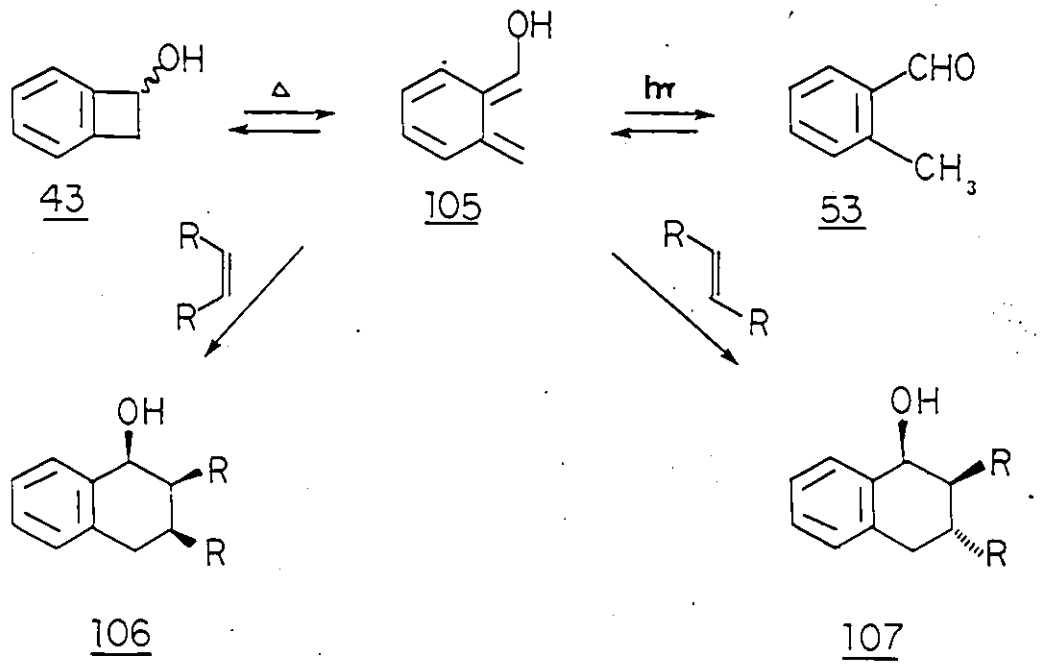


Todate, we have been unable to synthesize trans-2-aryl-1-hydroxy-4,5-(methylenedioxy)benzocyclobutene 83, which should serve as the starting material for a short, stereoselective synthesis of (±)-podophyllotoxin 6. Methods of generating 83 other than the o-bromostyrene oxide route are currently being investigated in our laboratory.

B. Intermolecular Approach to Podophyllotoxin Analogues: Synthesis of (±)-epiisopodophyllotoxin.

i. Introduction

It is well known that photolysis of 2-methylbenzaldehyde 53 and thermolysis of benzocyclobutenol 43 lead to the same dienol intermediate 105 which can be trapped with a variety of dienophiles to afford products such as 106 and 107, depending on the nature of the dienophile (Scheme 18).[64]

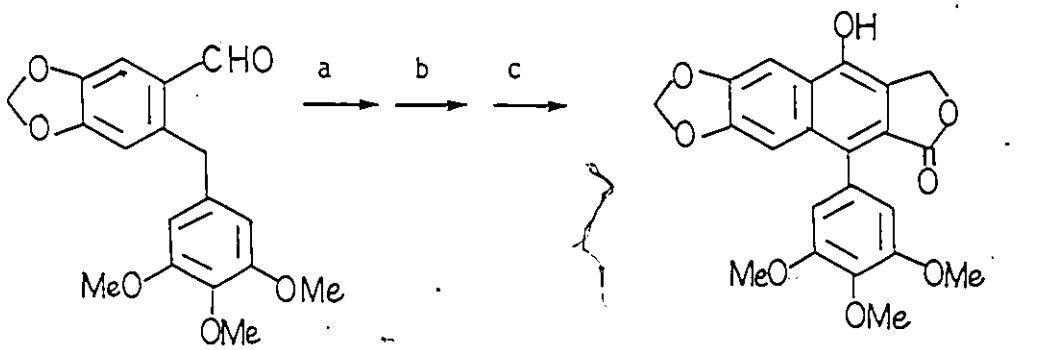


106 107

SCHEME 18

Ullman first demonstrated the intermediacy of the dienol species 105 in the photolysis of 2-methylbenzaldehyde[65] and Yang and Rivas illustrated the cycloaddition reaction of 105 with dienophiles,[66] but the bulk of information concerning the enolisation of ortho-alkyl-substituted aromatic carbonyl compounds has come from the work of Sammes and his co-workers.[67]

A number of workers have recognized the synthetic potential of the photoenolisation reaction, particularly as an entry into the aryl lignan systems.[68,69] Sammes used the adduct 108 resulting from trapping of the dienol obtained by photolysis of aldehyde 109 with dimethylacetylene dicarboxylate as a common intermediate in the synthesis of taiwanins E 110 and C 111 and justicidin E 112 (Scheme 19). In an analagous fashion aldehyde 109, prepared in seven steps and an overall yield of less than 10% starting with 6-bromopiperonal, was converted to tetradehydropodophyllotoxin 113.

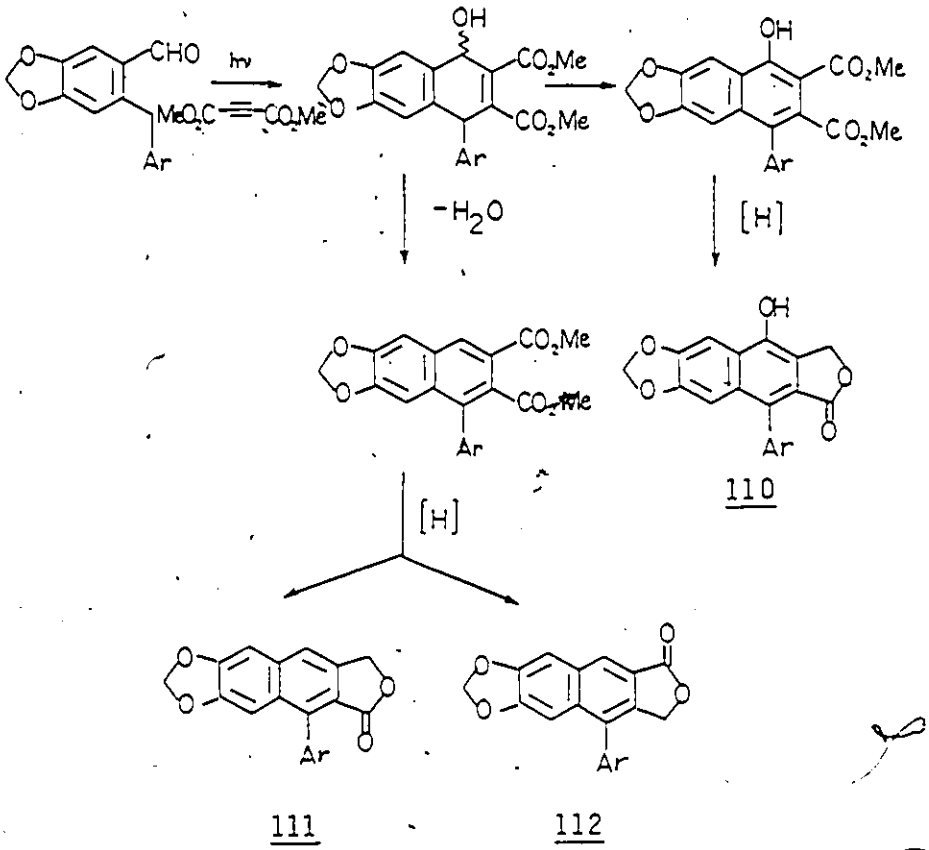


109 113 (13%)

a. hν, THF, $MeO_2C-\equiv-CO_2Me$

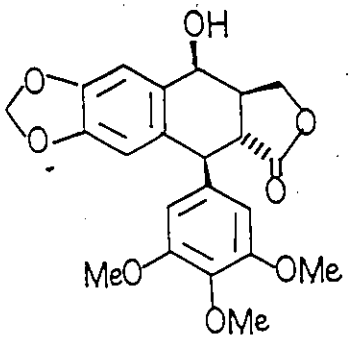
b. MnO_2

c. $NaBH_4$, MeOH, H^+



SCHEME 19

This section of the thesis will describe the work completed in the investigation of the use of the photoenolisation and subsequent cycloaddition reactions of o-alkylbenzaldehydes as key steps in the synthesis of podophyllotoxin analogues. The total synthesis of (±)-epiisopodophyllotoxin 114 will be described.

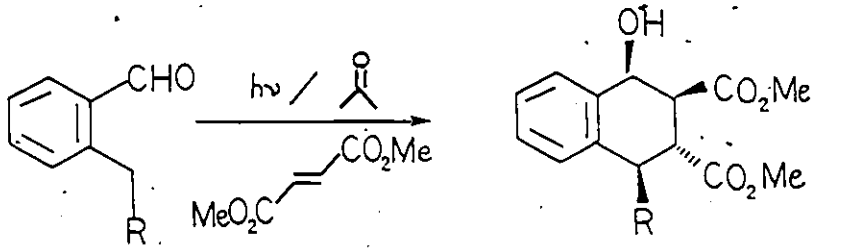


114

ii. Results and Discussion

The feas bility of the project was studied using two simple model systems chosen for the availability of starting materials and their basic resemblance to the "real" system under investigation. Thus, o-methylbenzaldehyde 53 and o-benzylbenzaldehyde 115, prepared from commercially available o-benzylbenzyl alcohol via PCC oxidation, were chosen as starting materials.

Irradiation of 53 and 115 in the presence of dimethyl fumarate with acetone as the solvent using a medium-pressure mercury arc gave after purification by column chromatography 116 and 117, respectively, as the only isolable photoadducts.

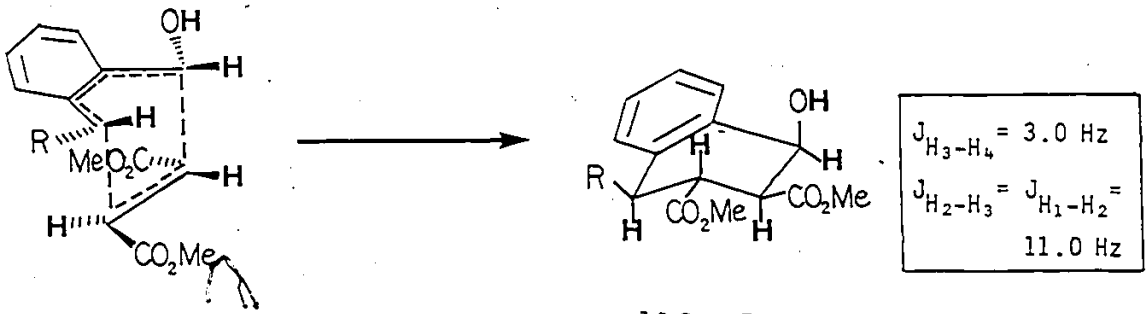


53 R=H
115 R=Ø

116 R=H (78%)
117 R=Ø (51%)

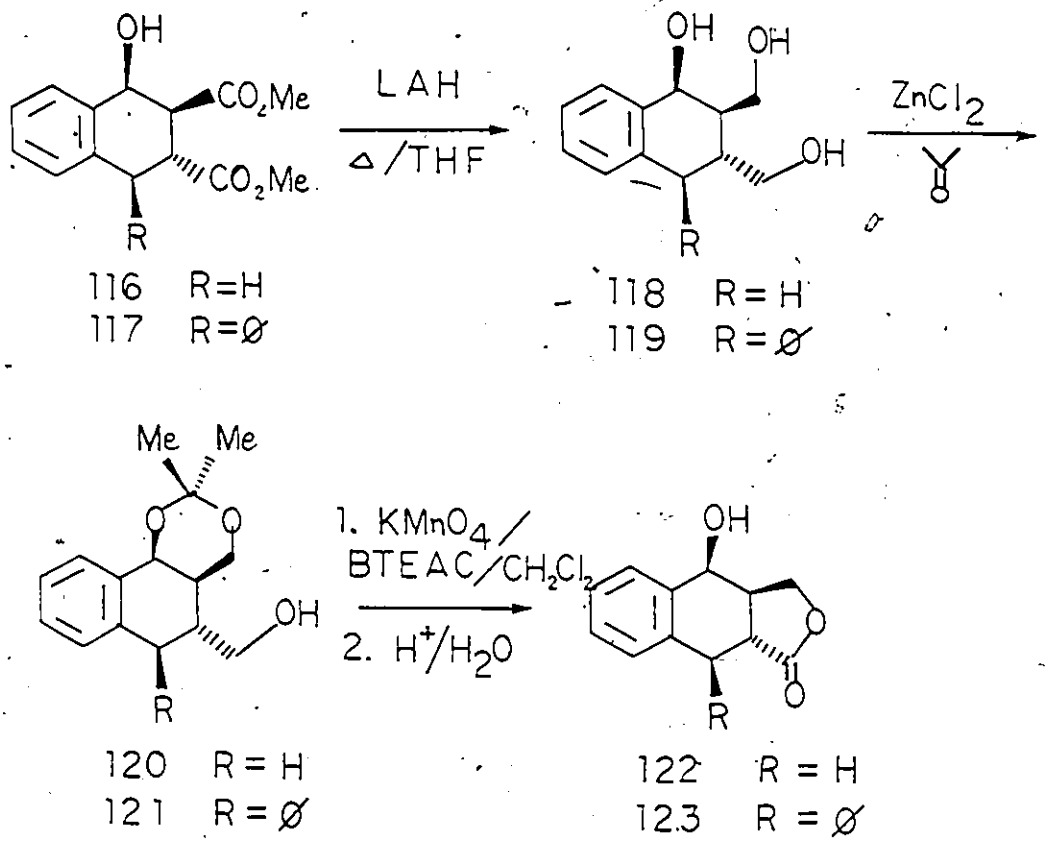
The relative stereochemistry of these adducts (116 and 117), where the substituents at C_1, C_2 and C_4 are cis to each other and the substituent at C_3 is trans to the others, was assigned on the basis of the ^1H nmr spectra. The measured value of $J_{H_3-H_4}$

was 3.0 Hz, consistent with a pseudo-axial, pseudo-equatorial relationship between H_3 and H_4. Both $J_{H_1-H_2}$ and $J_{H_2-H_3}$ are equal to 11.0 Hz , confirming the pseudo-diaxial relationships between H_1-H_2 and H_2-H_3.



116 R = H
117 R = Ø

These photoadducts must arise from endo addition (with respect to the hydroxyl group) of dimethyl fumarate to the (E,E)- dienol intermediate (Scheme 20). This is the expected result as predicted by the "endo rule". Woodward and Hoffmann,1965, showed that endo addition is energetically more favorable, on the basis of MO considerations, in the reaction of dienes with dienophiles.[76] This is especially the case for those dienophiles containing conjugated π-systems such as dimethyl fumarate.



116 R=H
117 R=Ø

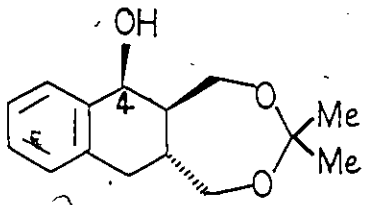
118 R=H
119 R=Ø

120 R=H
121 R=Ø

122 R=H
123 R=Ø

SCHEME 21

Scheme 21 outlines our first approach for the conversion of the photoadducts 116 and 117 to the corresponding trans-γ-lactones 122 and 123, respectively. The diesters 116 and 117 were reduced with lithium aluminum hydride (LAH) in dry THF to the corresponding triols 118 (mp 96-98° , methanol/ether) and 119 (mp 134-135°, ether/hexanes) in yields of 79 and 80 % respectively. Both 118 and 119 showed strong hydroxyl absorptions in the IR at 3350 to 3550 cm^{-1}. The triols were treated with anhydrous zinc chloride in acetone for 24h to afford after purification the isopropylidene derivatives 120 (mp 111-113°, ether/petroleum ether; 79%) and 121 (mp 155.5-156.5°, ether/hexanes; 77%). Along with 120 a small amount (16%) of another isopropylidene derivative was obtained. The structure of this derivative 124 was tentatively assigned as the seven membered cyclic ketal shown below.



124

Compound 124 had an R_f on tlc greater than that of 120. This is consistent with the fact that a secondary alcohol is less polar and therefore more mobile on tlc than a comparable primary

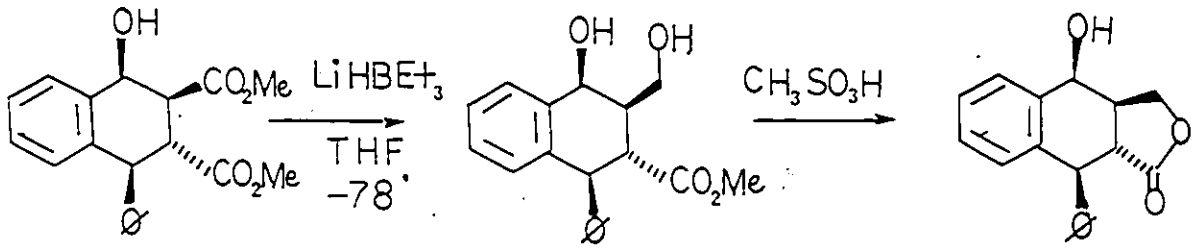
alcohol. The major difference in the ^1H nmr spectra of these two ketals was in the chemical shift of H_4, the benzylic hydrogen on the carbon bearing the oxygen moiety (C_4). A downfield shift of this peak in 120 (δ=4.98 ppm) when compared to 124 (δ=4.65 ppm) and the triol 118 (δ=4.78 ppm) was observed.

The alcohol 120 was oxidized by the method of Scholz[71] using $BnEt_3N^+MnO_4^-$ in CH_2Cl_2 to the corresponding acid, which was not isolated but under the acidic workup conditions deprotection and lactonization occured to afford, after purification by PTLC (ethyl acetate), the lactone 122 (mp 168°, ether/hexanes) in 62% yield. Similarly, 121 was converted to the corresponding lactone 123 (mp 193°, methylene chloride/hexanes) in 65% yield.

Both 122 and 123 showed strong absorptions in the IR at 1775 cm^{-1} representing the strained γ-lactone carbonyl and the appropriate molecular ion peaks in the mass spectra at m/e 204 ($C_{12}H_{12}O_3^{+\cdot}$) and m/e 280 ($C_{18}H_{16}O_3^{+\cdot}$), respectively. The ^1H nmr spectrum of 123 showed a multiplet at 2.75 ppm for H_3, a doublet of doublets at 3.33 ppm for H_2 ($J_{H_2-H_3}$=14.0 Hz, $J_{H_1-H_2}$=11.2 Hz), a doublet at 4.16 ppm for H_1 and a doublet at 4.86 ppm for H_4 ($J_{H_3-H_4}$=2.8 Hz). These coupling constants are consistent with the assigned stereochemistry where H_1, H_2 and H_3 are in a pseudo-axial position and H_4 is pseudo-equatorial.

We were able to improve the overall conversion of 117 to 123 by effecting a selective reduction of the C_3 ester group with $LiHBEt_3$ (Super-Hydride®)[72] in THF at -78°, furnishing the

crystalline diol 125, mp 95°, in 75% yield. The key ^{1}nmr peaks for 125 were : δ 4.24 (m, CH_2OH), 3.50 (s, CO_2CH_3), 2.53 (dd, J=11, 4 Hz, H_3), 3.08 (t, J=11 Hz, H_2), 3.76 (d, J=11 Hz, H_1) and 5.13 (d, J=4 Hz, H_4). The IR spectrum showed a strong ester carbonyl absorption at 1730 cm^{-1} and a hydroxyl absorption at 3300 to 3500 cm^{-1}. None of the isomeric diol was obtained. This selectivity for reduction of the less hindered ester group by $LiHBEt_3$ has been reported in the literature.[73] Lactonization of 125 to 123 was accomplished in 70% yield by treatment with methane sulfonic acid (CH_3SO_3H) in acetone.[74]

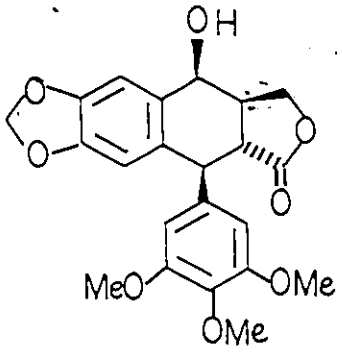


117 125 123

Synthesis of (±)-Epiisopodophyllotoxin

In application of the methodology above we have completed the synthesis of epiisopodophyllotoxin 114 (Scheme 24). This compound still contains the highly strained trans-fused lactone which is considered essential for biological activity, but the

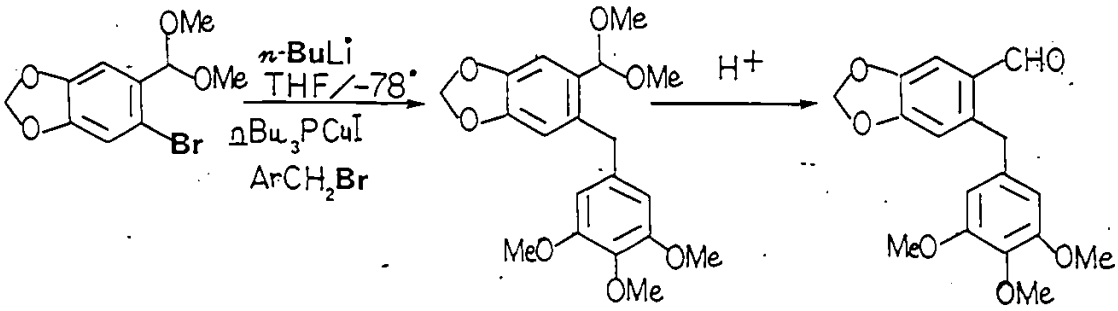
aryl substituent at C_1 and the lactone carbonyl group are in a trans relationship compared to a cis arrangement in podophyllotoxin. Epiisopodophyllotoxin has been mentioned briefly in the chemical literature[75] but a description of its synthesis has not been published.



114

A synthesis of the required aldehyde, 6-(3',4',5'-trimethoxybenzyl)piperonal, 109, had previously been reported by Sammes and co-workers[67] via a six step sequence with an overall yield of 27% utilizing 6-bromopiperonal ethylene ketal and 3,4,5-trimethoxybenzaldehyde as starting materials. We have found it possible to prepare 109 in 84% yield from 6-bromopiperonal dimethyl acetal 126[76] by treatment with n-BuLi at -78° in dry THF followed by n-Bu_3PCuI and then 3,4,5-trimethoxybenzyl bromide, warming to room temperature and stirring for 18h. The crude coupling product obtained after normal workup and column chromatography was deprotected using aqueous HCl in methanol

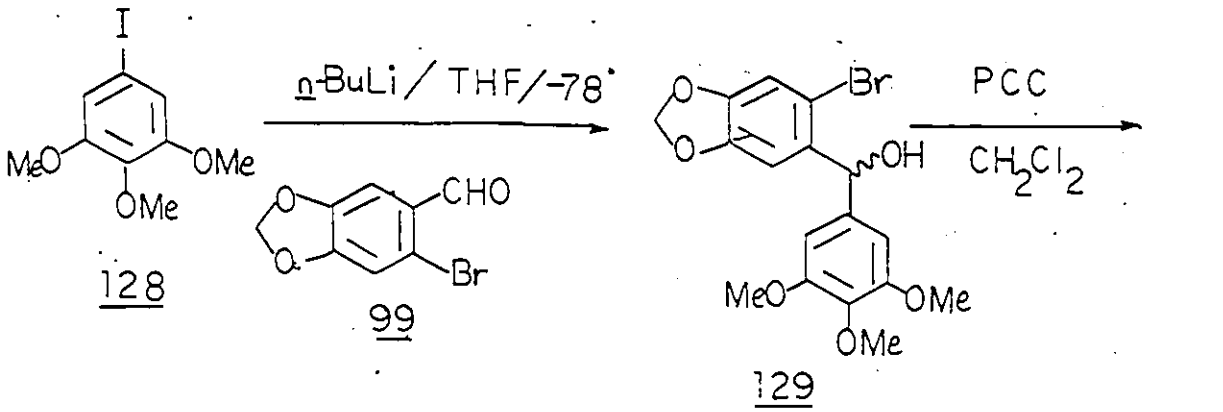
affording the desired aldehyde 109 as colorless needles. This coupling reaction is believed to occur via an aryl cuprate intermediate. Indeed, the use of n-Bu_3PCuI[77] was crucial for this reaction; no coupling was observed in its absence or when it was replaced by $MgBr_2$, $FeCl_3$ or $Pd(\phi_3P)_4$.



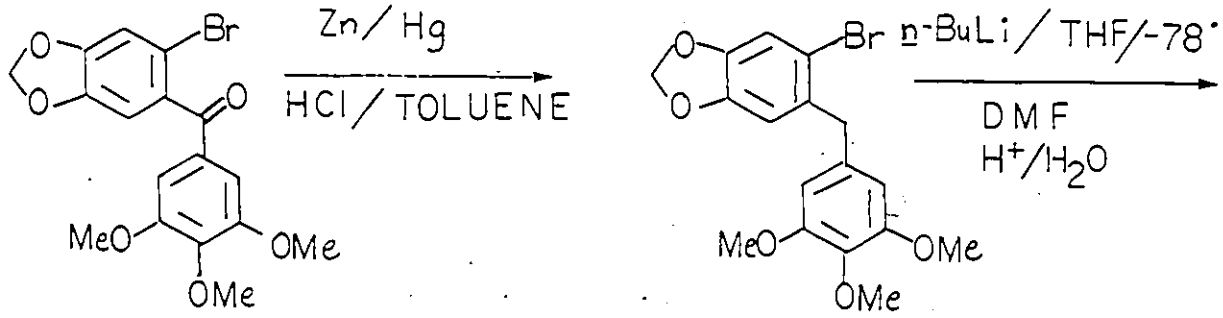
126 127 109

SCHEME 22

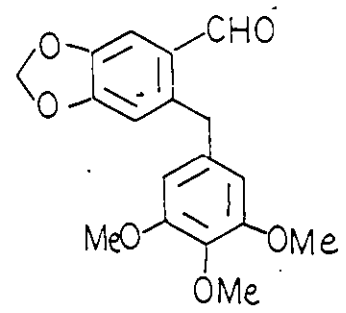
Our first synthesis of 109 involving a four step sequence starting with 1-iodo-3,4,5-trimethoxybenzene 128 and 6-bromopiperonal 99 and an overall yield of %, although inferior to the aforementioned "one-pot" scheme, will be discussed very briefly (Scheme 23). Halogen-lithium exchange of 1-iodo-



128 99 129



130 131

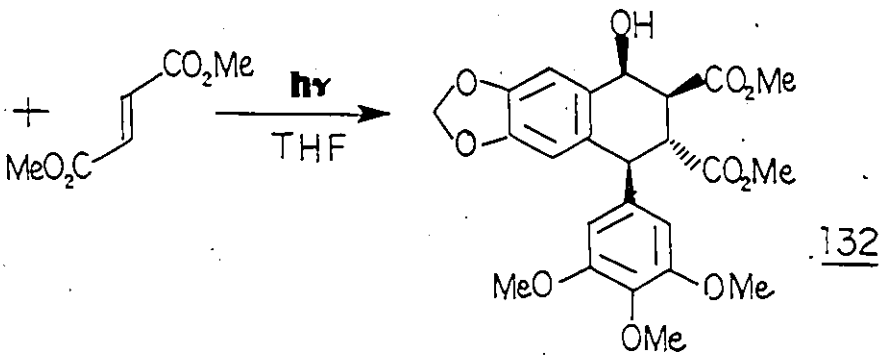


109

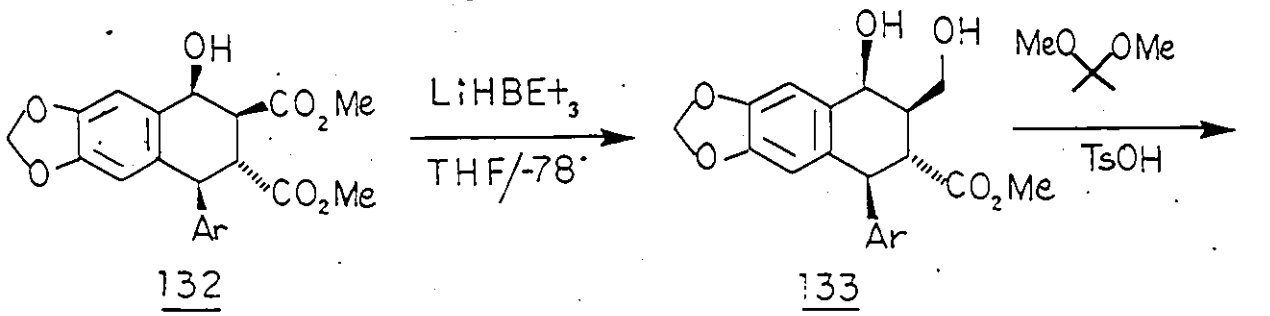
SCHEME 23

3,4,5-trimethoxybenzene 128 [79] with n-BuLi in THF at -78° followed by condensation with 6-bromopiperonal afforded the crude benzhydrol 129 which was oxidized with PCC[80] in CH_2Cl_2 furnishing 1-bromo-4,5-(methylenedioxy)-2-(3',4',5'-trimethoxybenzoyl)benzene 130, mp 150°, in an overall yield of 85%. The IR spectrum showed a carbonyl absorption at 1670 cm^{-1}, indicative of a conjugated ketone. Clemmensen reduction[81] furnished 1-bromo-4,5-(methylenedioxy)-2-(3',4',5'-trimethoxybenzyl)benzene 131 (mp 121-121.5°) in 77% yield. The benzylic methylene group is visible in the ^1H nmr spectrum as a singlet at 3.94 ppm. Conversion of 131 to the aldehyde 109 was brought about by halogen-lithium exchange and trapping of aryl anion with dimethylformamide (DMF), followed by hydrolysis to furnish 109 in 80% yield.

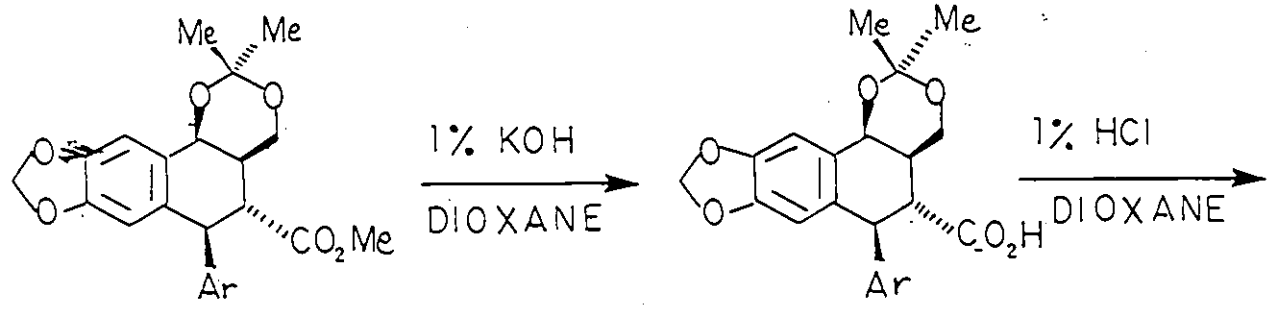
Irradiation of 109 in THF in the presence of dimethyl fumarate afforded the diester 132 (mp 198°) as the only isolable adduct in 47% yield. THF was found to be a better solvent for this particular reaction than acetone , acetonitrile or benzene. The low yield was believed to result from the instability of 132 which undergoes facile dehydration.



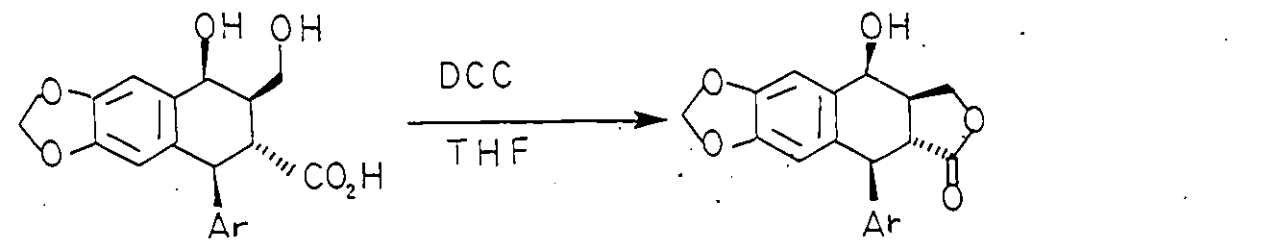
132



132 133

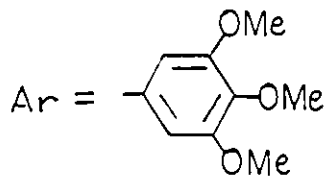


134 135



136 114

SCHEME 24



The ester group at C_3 in 132 was selectively reduced upon reaction with three equivalents of $LiHBEt_3$ in dry THF at -78° followed by warming to 25° and acid hydrolysis of the borate ester. The crystalline diol 133 (mp 155°, ether/hexanes) was obtained in 70% yield. We were unable to convert methyl epiisopodophyllate 133 directly to epiisopodophyllotoxin 114 by acid catalyzed lactonization or to saponify the ester moiety to produce epiisopodophyllic acid 136 in satisfactory yields. The instability of 133 and 136 are probably major factors in the failure of our efforts to perform these seemingly trivial transformations. Under a variety of conditions, extensive decomposition and / or aromatisation were the consequences.

This problem was circumvented by protecting the diol 133 as the isopropylidene derivative 134 (mp 181-182°, ether/hexanes) by treatment with 2,2-dimethoxypropane and TsOH, prior to carrying out a mild basic ester hydrolysis (1% aq. KOH/ dioxane), to furnish the acid 135 (mp 181-183°). Careful hydrolysis of the ketal moiety using a 1:1 mixture of 1% aqueous HCl and dioxane afforded epiisopodophyllic acid 136, mp 230-234°, dec., acetone/ether (lit.mp 228-230°.dec.)[82] in 65 % overall yield from 133.

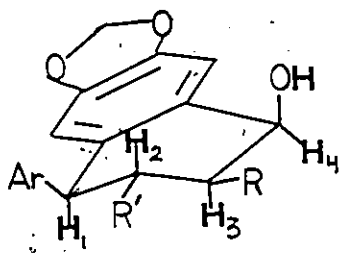
Lactonization of 136 to epiisopodophyllotoxin 114 , mp 258-260° (lit. mp 272° dec.)[75] was accomplished using DCC as the activating agent following the method of Renz, Kuhn and von Wartburg (1965) for the conversion of podophyllic acid to podophyllotoxin.[83]

The mass spectrum of 114 showed a strong molecular ion peak at m/e 414 and peaks of relatively lower intensity at m/e 399 ($M^+-CH_3^\cdot$), 397 ($M^+-OH^\cdot$), 351 ($M^+-OH^\cdot-CO_2$) and 168 ($C_6H_3(OCH_3)_3^{+\cdot}$). Selected ^1H nmr data for compounds 132 to 136 and 114 are summarized in Table 4, focusing on the nonaromatic protons.

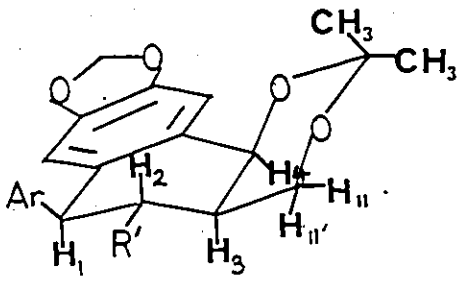
The nmr spectra of compounds 132, 133, 134, 135 and 136 are very similar especially with respect to the hydrogens on the B ring (H_1, H_2, H_3 and H_4). The consistency observed in the values of the coupling constants $J_{H_1-H_2}$, $J_{H_2-H_3}$ and $J_{H_3-H_4}$, where the deviation of these values is less than 1 Hz, shows that the stereochemistry of the original photoadduct 132 has been retained throughout all the chemical manipulations. The coupling constants, $J_{H_1-H_2}$ and $J_{H_2-H_3}$ range from 10.5 to 12.0 Hz and are consistent with pseudo-diaxial arrangments of these hydrogens. The protons H_3 and H_4 are in a pseudo-axial, pseudo-equatorial arrangement and the value of $J_{H_3-H_4}$ (3.0 Hz) confirms this relationship.

The ^1H nmr data for epiisopodophyllotoxin was compared to that published for a series of known podophyllotoxin derivatives.[84] The relative stereochemistry at C_2, C_3 and C_4 is the same as in epipodophyllotoxin 137 and the coupling constants $J_{H_2-H_3}$ and $J_{H_3-H_4}$ compare very well (for 114 : $J_{H_2-H_3}$= 14.0, $J_{H_3-H_4}$=3.0; for 137 : $J_{H_2-H_3}$= 13.8, $J_{H_3-H_4}$= 3.0). The value for $J_{H_1-H_2}$ (10.0 Hz) is consistent with the pseudo-diaxial arrangement of these hydrogens.

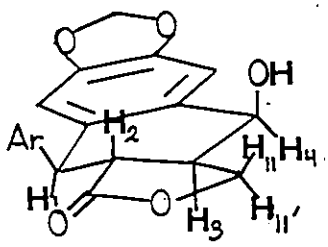
TABLE 4 : SELECTED NMR DATA FOR COMPOUNDS 132→136 and 114



A



B

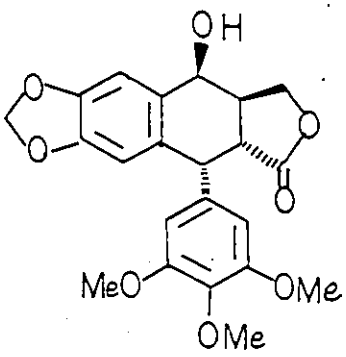


C

COMPOUND	STRUCTURE	δ (ppm)						J (Hz)					
		H_1	H_2	H_3	H_4	H_{11}	$H_{11'}$	J_{1-2}	J_{2-3}	J_{3-4}	$J_{11-11'}$	J_{3-11}	$J_{3-11'}$
132	A; R=R'=CO_2Me	4.02	3.42	3.19	5.07	-	-	10.5	12.0	3.0	-	-	-
133	A; R=CH_2OH, R'=CO_2Me	a	3.00	2.45	5.01	a	a	11.0	11.0	3.0	a	a	a
134	B; R'=CO_2Me	4.06	3.40	2.03	4.83	4.18	3.65	11.6	11.6	3.0	12.0	3.5	2.0
135	B; R'=CO_2H	4.01	3.48	2.01	4.81	4.09	3.69	11.6	11.6	3.0	12.0	3.5	2.0
136	A; R=CH_2OH, R'=CO_2H	a	3.08	2.47	5.07	a	a	11.0	11.0	3.0	a	a	a
114	C	4.03	3.29	2.68	4.94	4.11	4.46	10.0	14.0	3.0	a	a	a

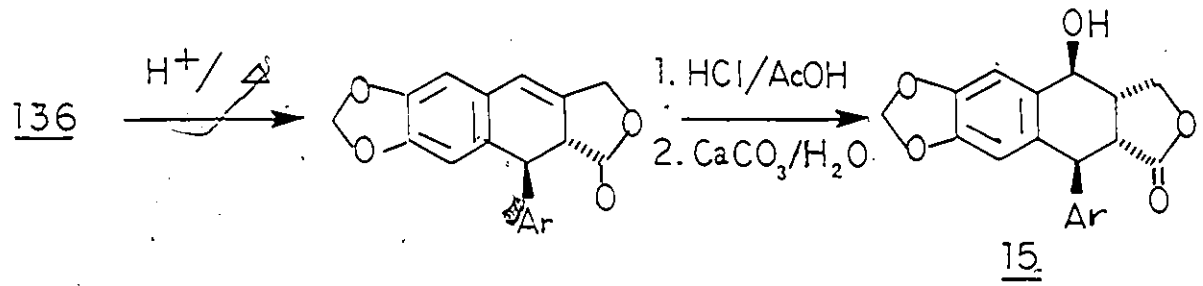
Ar = 3,4,5-trimethoxybenzene

a) These values were not accurately measureable.



137

(±)-Epiisopodophyllic acid 136 has been converted to (±)-picropodophyllotoxin 15 in a total of three steps involving dehydration, lactonization and rehydration[82] (Scheme 25). Thus, our synthesis of epiisopodophyllic acid constitutes a formal synthesis of (±)-picropodophyllotoxin and (±)-podophyllotoxin since Gensler has converted the former into the latter.



SCHEME 25

Ar = 3,4,5-TRIMETHOXY-BENZENE

RESULTS AND DISCUSSION

PART 2

SYNTHESIS OF NON-ENOLISABLE PODOPHYLLOTOXIN DERIVATIVES

i. Introduction

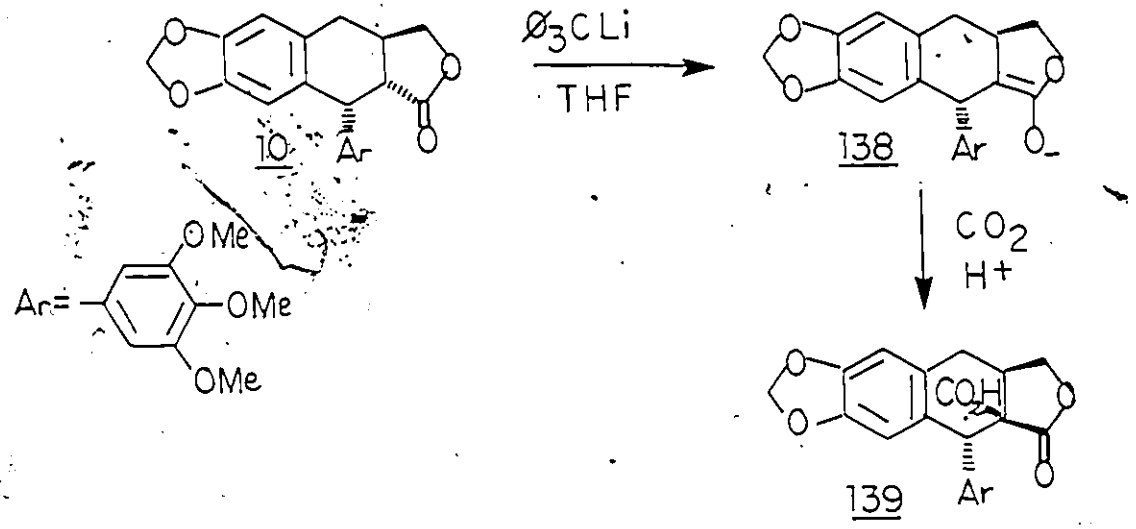
The epimerization of podophyllotoxin to picropodophyllotoxin is thought to occur under physiological conditions.[85] The biological activity of picropodophyllotoxin as well as other cis analogues is either much lower than that of the trans isomers or is negligible.[86] It appears that epimerization may be the primary method of detoxification by the cell.

The reversibility of this reaction was discussed in the Introduction. Gensler suggested that the low level activity observed for picropodophyllotoxin might be due to the small amounts of podophyllotoxin generated by equilibration.[28] It seems unlikely that under the neutral conditions of the tubulin binding assay that epimerization could occur since there have been no reports of an interconversion other than that by base.

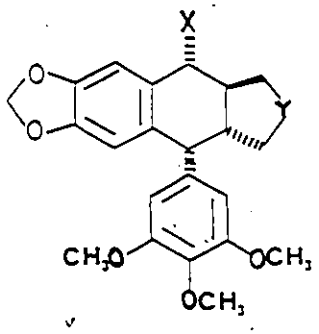
Gensler modified this suggestion based on the results of 60 MHz and 360 MHz ^{1}H nmr studies of both Ayres and Brewer.[84,87]

Picropodophyllotoxin can exist with the trimethoxybenzene ring (E- ring) in an equatorial or quasi-axial conformation. Gensler proposed that the residual activity may be due to the minor, quasi-axial conformation which places the E-ring in approximately the same orientation found in podophyllotoxin.

From the chemotherapeutic point of view, the epimerization is undesirable , since limiting the physiological lifetime of the drug would set an upper limit to their biological effectiveness. Gensler decided to approach this problem by synthesizing derivatives in which epimerization was precluded. Unfortunately he was unable to replace the hydrogen at the C_2 position with a suitable substituent and retain the trans-fused γ-lactone. Treatment of 4-deoxypodophyllotoxin 10 with triphenylmethyl lithium produced the enolate 138 which was carboxylated with carbon dioxide to give 2-carboxydeoxypicropodophyllotoxin 139.[88]



Discouraged by these preliminary results Gensler turned his attention towards blocking the enolization mechanism by eliminating the lactone group altogether. He prepared a series of "delactonized" derivatives 140 in which the carbonyl group has been reduced to methylene and the lactone oxygen was replaced by a variety of functions: S, SO_2, CO and CH_2.[89] None of these compounds proved to be more effective than podophyllotoxin or deoxypodophyllotoxin.[90]



X = H, OH.

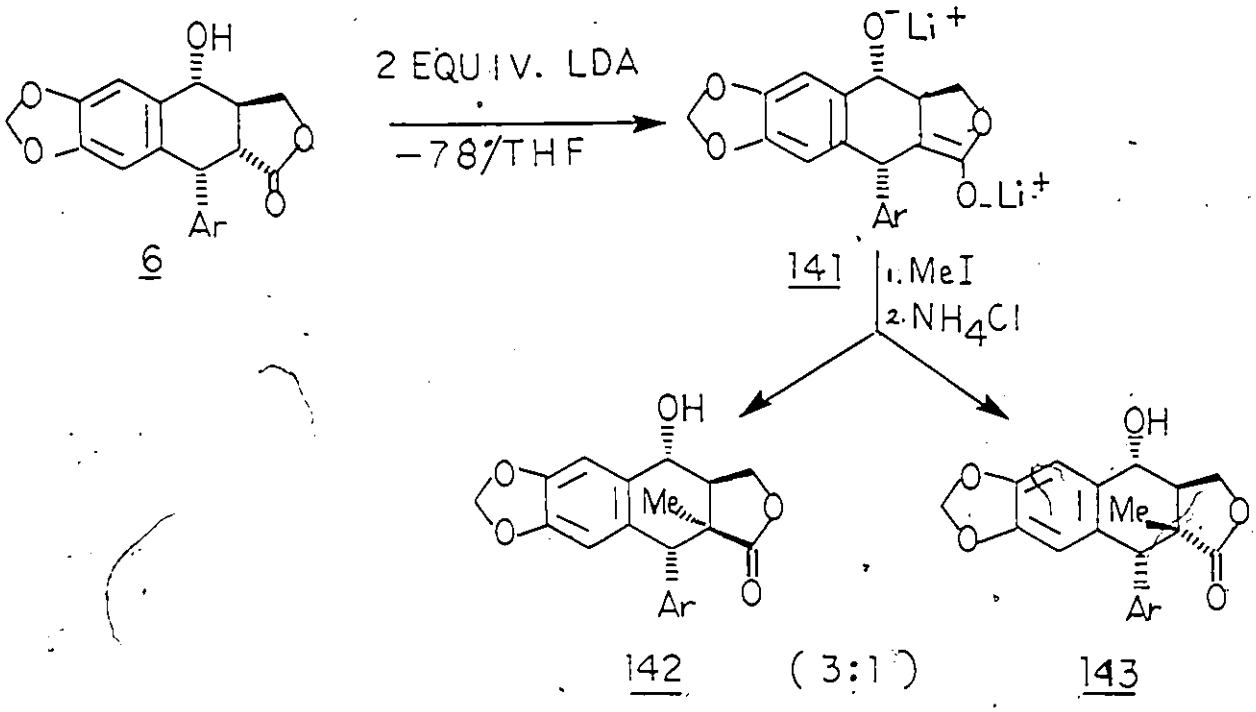
Y = O, S, SO_2, CO, CH_2.

140.

ii. Results and Discussion

Dissatisfied with the results of Gensler's study we decided to reinvestigate the problem of synthesizing C_2-substituted podophyllotoxin derivatives via the enolate anion. The dianion 141

of podophyllotoxin was prepared by treatment of podophyllotoxin 6 with two equivalents of LDA at -78° in dry THF. The enolate was reacted with excess methyl iodide at -78°, warmed to room temperature and stirred for an additional 18 h. Normal workup and HPLC (hexanes/ethyl acetate, 1:1) furnished a 3:1 mixture of 2-methylpicropodophyllotoxin* 142 and 2-methylpodophyllotoxin 143, respectively, in an overall yield of 71%. Thus, under these conditions the desired product 143 (the one retaining the trans-lactone) was obtained as the minor component.

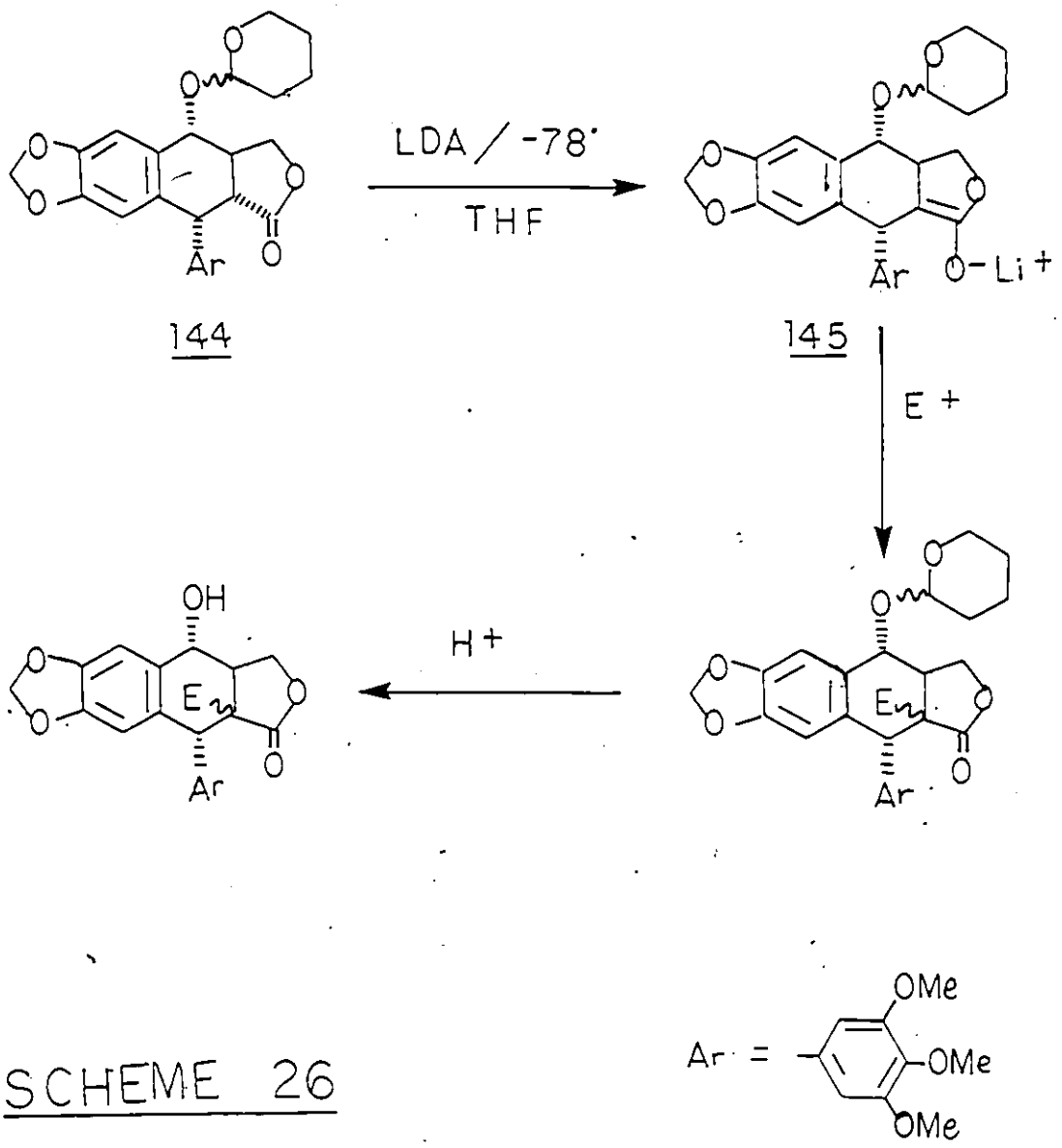


* Nomenclature The following nomenclature has been adopted for the substituted derivatives of podophyllotoxin. Derivatives having the same stereochemistry at carbons 2 and 3 as podophyllotoxin are named as being derived from the same. Similarly, derivatives having the same stereochemistry at carbons 2 and 3 as picropodophyllotoxin are named as being derived from picropodophyllotoxin.

Since Gensler had obtained better results with proton trapping of the 4-O-tetrahydropyranylpodophyllotoxin enolate anion than with the dianion we turned our attention to this route (Scheme 26). Treatment with dihydropyran in the presence of TsOH converted podophyllotoxin to 4-O-tetrahydropyranyl-podophyllotoxin 144 in good yield.

The enolate 145 was formed by treatment of 144 with 1.1 equivalents LDA at -78° in dry THF. Trapping of the enolate with methyl iodide (-78° to rt, 18 h) gave after workup a mixture of tetrahydropyranyl derivatives. The crude product was exposed directly to the action of aqueous acid to remove the protecting group. Normally the C_2 substituted tetrahydro-pyranyl derivatives were not isolated because of the added complication due to the presence of additional diastereomers caused by the tetrahydropyranyl ring. HPLC (hexanes/ethyl acetate, 1:1) effected a clean separation and afforded 2-methylpodophyllotoxin 143 and 2-methylpicropodophyllotoxin 142 in yields of 43 and 19%, respectively.

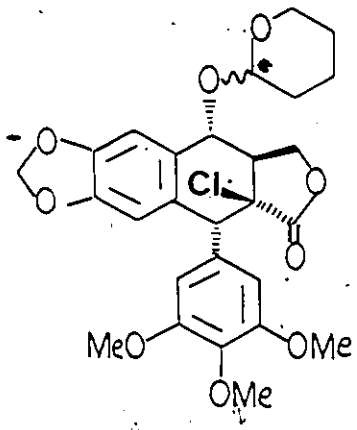
Similarly, treatment of the enolate 145 with dry oxygen for 30 minutes at -78° followed by reduction of the intermediate hydroperoxides with aqueous sodium sulfite gave after removal of the tetrahydropyranyl group a 1:1 inseparable mixture of 2-hydroxypodophyllotoxin 146 and 2-hydroxypicropodophyllotoxin 147 in 84% yield. This difference in stereochemical outcome can be explained on the basis of mechanistic differences in the reaction



SCHEME 26

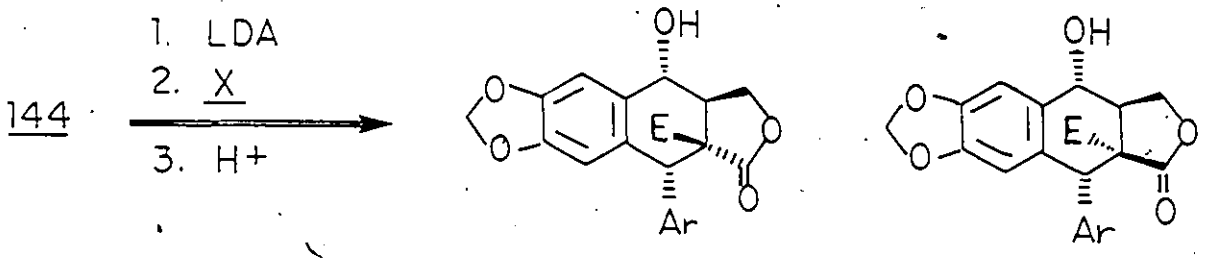
of carbanions with alkyl halides and with oxygen. The latter reaction is an electron transfer process involving a radical intermediate.[92]

The best stereochemical result was obtained with chlorination of the enolate 145 by reaction with excess hexachloroethane (-78° to rt , 18h) where only one product was obtained after removal of the protecting group. Chromatography (hexanes/ethyl acetate, 1:1) afforded 2-chloropodophyllotoxin 148 in 74% yield. In this case the tetrahydropyranyl derivative was also isolated and characterized. 2-Chloro-4-O-tetrahydropyranylpodophyllotoxin 149 was obtained as a 3:2 mixture of diastereomers[93] (due to the presence of a chiral center in the THP portion) after precipitation from ether/hexanes. The mass spectrum and 360 MHz ^1H nmr spectrum of 149 are shown in Figures 5 and 6 , respectively. The results of the enolate trapping experiments are summarized in Table 5.



149 3:2 MIXTURE OF DIASTERIOMERS

TABLE 5



E = CH_3 143
OH 146
Cl 148

E = CH_3 142
OH 147

X	E	PRODUCTS AND YIELDS	RATIO PODO/PICRO
CH_3I	CH_3	143 (43%) 142 (18%)	2.4/1
O_2	OH	146 + 147 (84%)	1/1
Cl_3CCCl_3	~~Cl~~	148 (74%)	-

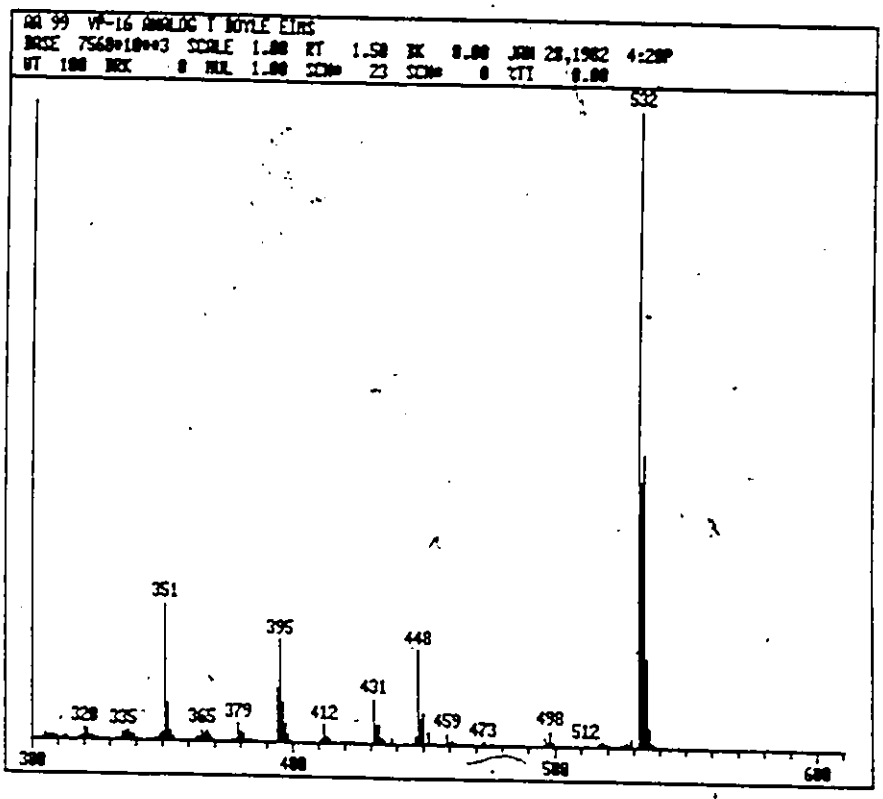


FIGURE 5 MASS SPECTRUM OF COMPOUND 149

PROPOSED M.S. FRAGMENTATION PATHWAY FOR 149

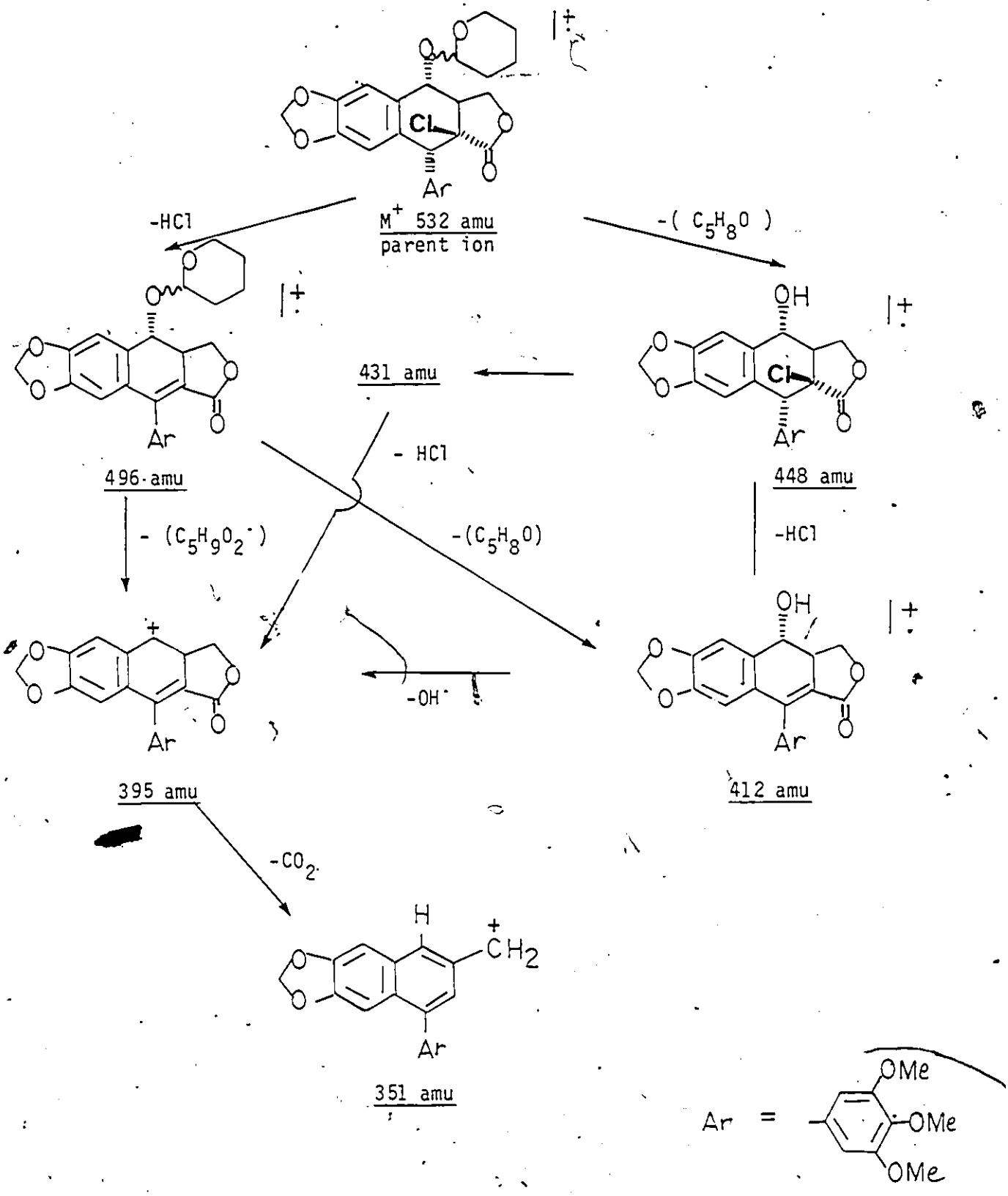
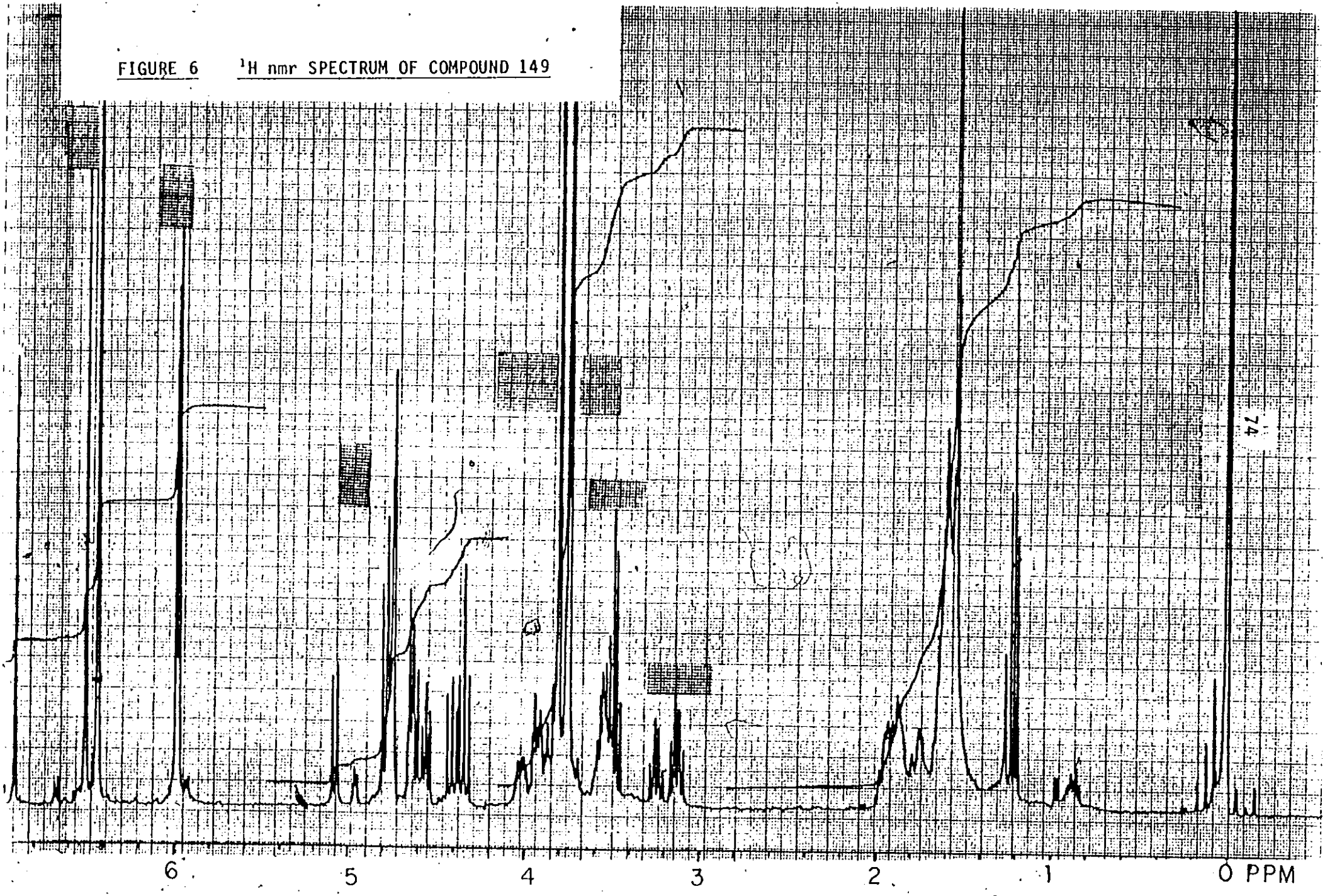


FIGURE 6 ^{1}H nmr SPECTRUM OF COMPOUND 149



The structures of the C_2-substituted podophyllotoxin derivatives were assigned on the basis of their 360 M Hz ^1H nmr spectra. The nmr data for these compounds are summarized in Tables 6 and 7. Substitution at C_2 was clearly evident by the presence of a sharp singlet for H_1 at 4.26 ppm, 4.23 ppm and 4.79 ppm, in 143, 142 and 148, respectively.

The stereochemistry at C_2 was assigned on the basis of the values of the coupling constants $J_{H_3-H_{11}}$ and $J_{H_3-H_{11}'}$. The numerical values for the constants are lower in picropodophyllotoxin ($J_{H_3-H_{11}}$ = 1.5 Hz and $J_{H_3-H_{11}'}$ = 6.0 Hz) than in podophyllotoxin ($J_{H_3-H_{11}}$ = 9.0 Hz and $J_{H_3-H_{11}'}$ = 8.0 Hz.[84]

The aromatic protons show a characteristic three signal pattern in the nmr which is dependent on the stereochemistry of the lactone ring. It was observed that in the trans (podo) series the two singlets for the methylenedioxybenzene protons (H_5 and H_7) were consistently downfield from the two proton singlet representing the trimethoxybenzene protons ($2\times H_8$). The chemical shifts for H_5, H_7 and H_8 were 7.11, 6.51, 6.37 (podophyllotoxin); 7.10, 6.48, 6.36 (2-methylpodophyllotoxin); 7.09, 6.49, 6.44 (2-chloropodophyllotoxin) and 7.10, 6.49, 6.38 (2-hydroxypodophyllotoxin. In the cis (picro) series the two proton singlet for the trimethoxybenzene protons was slightly downfield from the H_7 signal. The observed chemical shifts for H_5, H_8 and H_7 were 7.05, 6.45, 6.38 (picropodophyllotoxin); 6.76, 6.78, 6.65 (2-methylpicropodophyllotoxin) and 7.04, 6.45, 6.38 (2-hydroxy-

^{1}H NMR DATA FOR THE 2-SUBSTITUTED PODOPHYLLOTOXIN DERIVATIVES

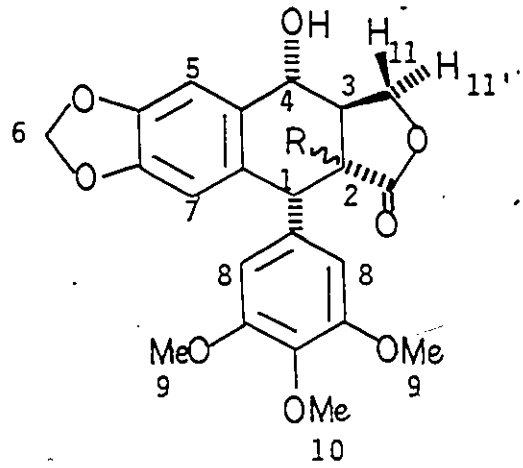


TABLE 6 CHEMICAL SHIFTS

COMPOUND	H_1	H_3	H_4	H_5	H_6	$H_{6'}$	H_7	H_8	H_9	H_{10}	H_{11}	$H_{11'}$
6	4.59	2.77	4.77	7.11	5.98	5.98	6.51	6.37	3.75	3.81	4.09	4.60
143	4.26	2.89	4.70	7.10	5.97	5.98	6.48	6.36	3.75	3.81	4.17	4.51
148	4.79	3.07	4.98	7.09	5.97	5.99	6.49	6.44	3.77	3.84	a	a
146	a	a	a	7.10	a	a	6.49	6.38	3.74	3.83	a	a
147	a	a	a	7.04	a	a	6.34	6.46	3.79	3.87	a	a
15	4.11	2.79	4.51	7.05	5.94	5.94	6.38	6.45	3.78	3.85	4.44	4.53
142	4.23	2.79	4.57	6.76	5.94	5.96	6.65	6.78	3.79	3.80	a	a

a ~ not measurable with accuracy

TABLE 7 COUPLING CONSTANTS

COMPOUND	$J_{H_3-H_4}$	$J_{H_3-H_{11}}$	$J_{H_3-H_{11'}}$	$J_{H_{11}-H_{11'}}$	$J_{H_6-H_{6'}}$
6	9.1	9.0	8.0	8.8	0.5
143	11.0	10.5	7.5	9.0	0.5
148	9.5	9.0	7.0	a	0.5
15	8.3	1.5	6.0	10.2	0.5
142	7.8	1.4	6.0	a	0.5

picropodophyllotoxin).

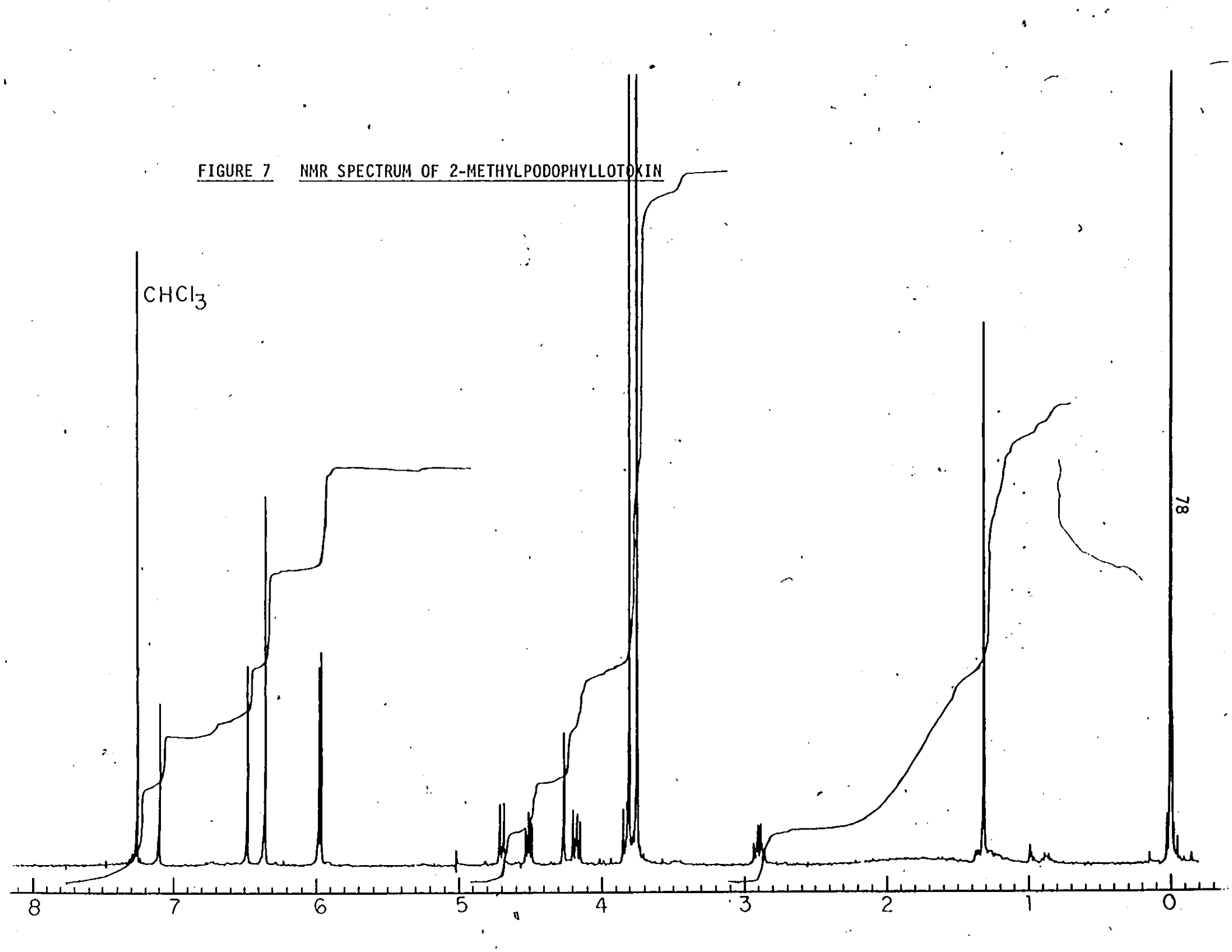
All other data collected for compounds 142, 143, 146, 147 and 148 were in agreement with the assigned structures (see Experimental Section). The nmr spectra of 2-methylpodophyllotoxin 143 and 2-chloropodophyllotoxin are given in figures 7 and 8 as representative examples.

Biological testing against either Leukemia L1210 or P388 was performed on the C_2 substituted derivatives (142, 143, 146 147 and 148) at the antitumour division of Bristol Laboratories, Syracuse, New York. The general testing protocol was as follows.[94] Ascitic fluid containing 10^6 cells was implanted intraperitonealy in female CDF_1 mice (six mice per test group). Treatment began 24 hours after implant and the parameter was median survival time. Results are given as percent increased survival time of test group over control group (% T/C). An initial T/C $\geq$ 125 is considered significant antitumour activity.

The results are shown in Tables 8 and 9. The methyl derivatives 142 and 143 were inactive both in the L1210 and P388 tests. The mixture of hydroxyl derivatives 146 and 147 was toxic, having a T/C of less than 85 , as was podophyllotoxin itself under these testing conditions. Interestingly, 2-chloropodophyllotoxin 148 had a level of antitumour activity against P388 substantially above the accepted significant level (T/C = 156).

Encouraged by the promising result with the chloro-derivative and knowing that the glycoside moiety , as found in VP-16 , is required for lower toxicity and high activity , we decided to

FIGURE 7 NMR SPECTRUM OF 2-METHYLPODOPHYLLOTOXIN



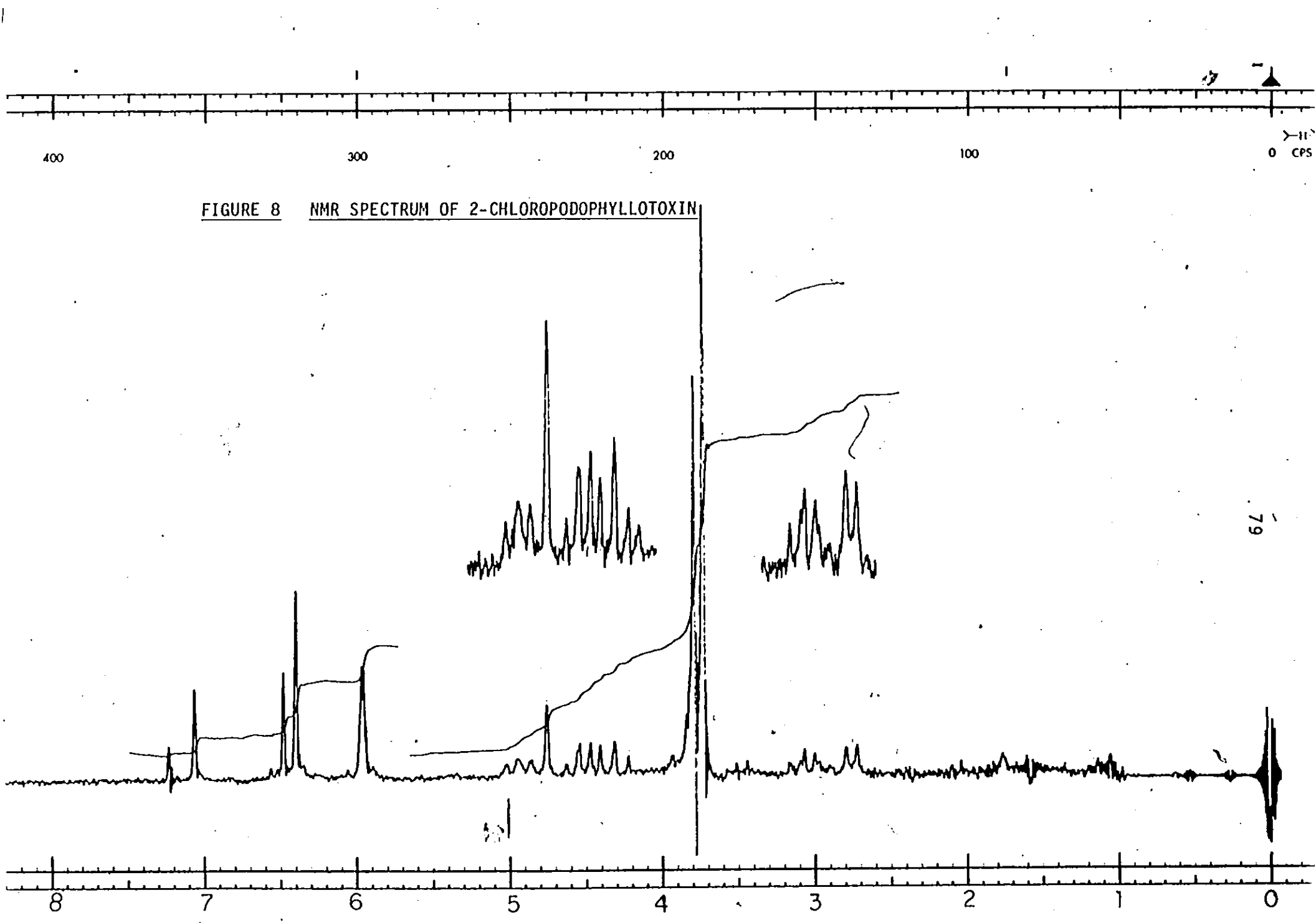


FIGURE 8 NMR SPECTRUM OF 2-CHLOROPODOPHYLLOTOXIN

TABLE 8 : EFFECT OF PODOPHYLLOTOXIN DERIVATIVES ON P388 LEUKEMIA

MATERIAL	TREATMENT SCHEDULE	DOSE IP mg/kg/inj	MST DAYS	EFFECT MST %T/C	AWC gm d.6	SURVIVORS DAY 5
NSC 38270	d.1→5	0.8	13.0	144	-0.5	6/6
		0.4	12.5	139	-0.6	6/6
VP-16 (24)	d.1&5	40	>30.0	>333	-1.8	6/6
		20	>30.0	>333	-1.7	6/6
VM-26 (25)	d.1&5	40	>30.0	>333	-1.4	6/6
		20	26.0	289	-0.6	6/6
143	d.1&5	120	9.0	100	+1.8	6/6
		60	8.0	89	+2.7	6/6
		40	8.5	94	+2.2	6/6
		20	8.0	89	+2.4	6/6
		10	8.0	89	+3.5	6/6
		5	9.0	100	+3.3	6/6
146&147	d.1&5	80	TOX	TOX	TOX	2/6
		40	TOX	TOX	TOX	3/6
		20	10.0	111	-0.9	6/6
		10	9.0	100	-0.1	6/6
148	d.1&5	40	14.0	156	-2.8	5/6
		20	11.0	122	-1.0	5/6
		10	9.0	100	+0.6	6/6
		5	9.0	100	0	6/6
PODOPHYLLO-TOXIN 6	d.1&5	60	TOX	TOX	TOX	0/6
		30	TOX	TOX	TOX	1/6
		15	10.0	111	-0.1	6/6
		7.5	10.0	111	+0.7	6/6
CONTROL		SALINE	9.0	100	-0.5	10/10

Tumor inoculum: 10^6 ascites cells implanted ip.
Host : CDF_1 female mice.
TOX : <4/6 mice alive on Day 5.
Evaluation : MST = median survival time.
Effect : %T/C = (MST treated / MST control) × 100
Criteria : %T/C > or = 125 considered significant antitumor activity.

TABLE 9 EFFECT OF PODOPHYLLOTOXIN DERIVATIVES ON LEUKEMIA L1210

MATERIAL	TREATMENT SCHEDULE	DOSE IP mg/kg/inj	MST DAYS	EFFECT MST %T/C	AWC gm d.6	SURVIVORS DAY 5
VP-16	d.1&5	45	20.0	286	-2.8	6/6
		30	18.0	257	-3.1	6/6
142	d.1&5	45	7.0	100	+0.7	6/6
		30	7.0	100	+0.2	6/6
		15	7.0	100	+0.9	6/6
		7.5	7.0	100	+0.5	6/6
142&143	d.1&5	60	7.0	100	-1.0	6/6
		45	7.0	100	+0.2	6/6
		30	7.0	100	+1.0	6/6
		15	6.0	86	+1.0	6/6
CONTROL		saline	7.0	-	+0.6	10/10

TABLE 10 EFFECT OF VP-16 DERIVATIVES ON LEUKEMIA P388

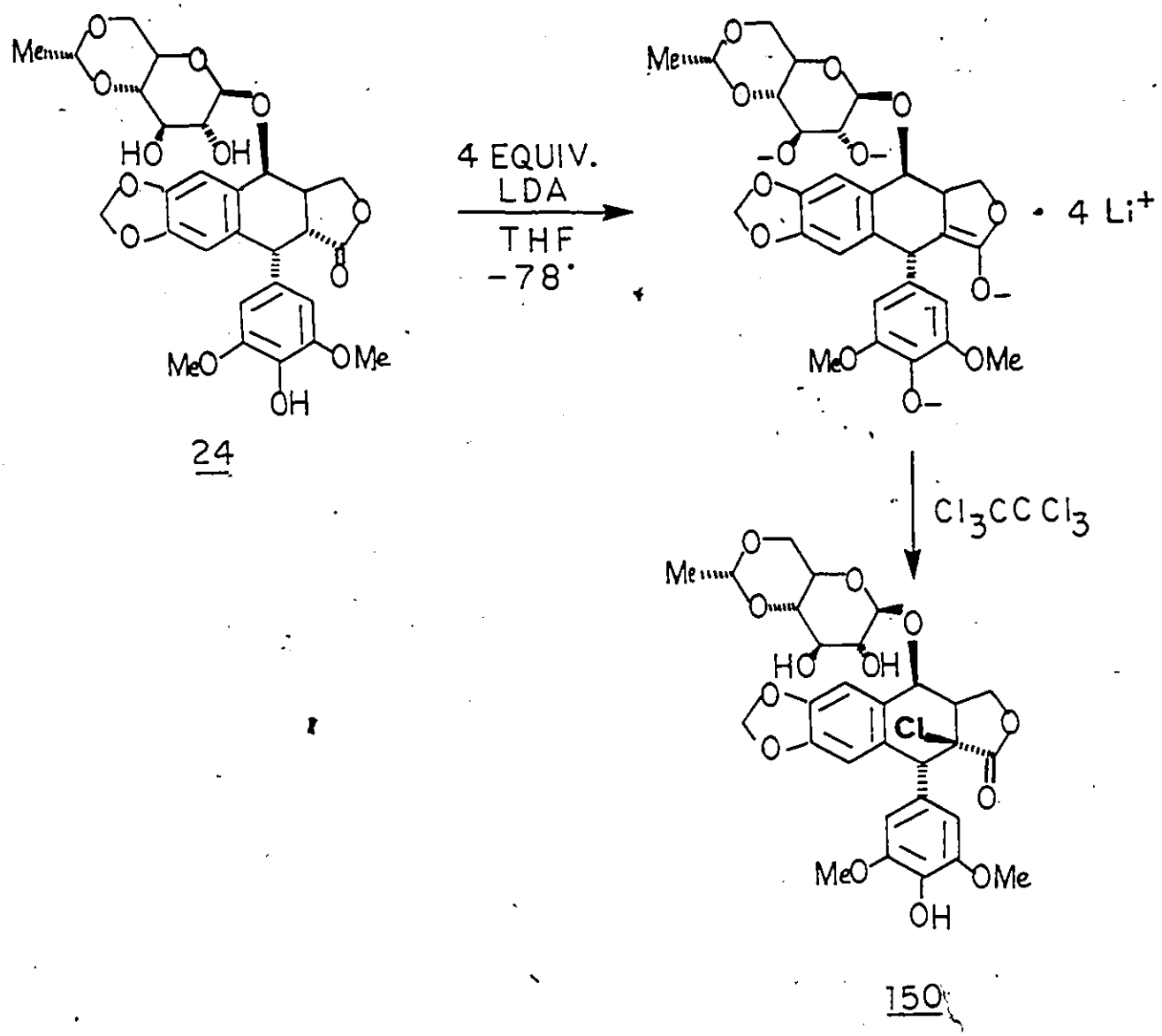
MATERIAL	TREATMENT SCHEDULE	DOSE IP mg/kg/inj	MST DAYS	EFFECT MST %T/C	AWC gm d.6	SURVIVORS DAY 5(45)
VP-16	d.1&5	40	>45.0	>500	-2.2	6/6 (4)
			>45.0	>500	-1.4	6/6 (4)
150	d.1&5	60	>45.0	>500	-1.8	6/6 (5)
		30	29.0	322	-1.2	6/6 (2)
		15	21.4	239	-1.0	6/6
		7.5	16.0	178	-0.3	6/6
CONTROL		saline	9.0	-	-0.5	10/10

Tumor inoculum : 10^6 ascites cells implanted ip.
Host : CDF_1 female mice.
Evaluation : MST^1 = median survival time.
Effect : %T/C = (MST treated / MST control) × 100.
Criteria : %T/C > or = 125 considered significant antitumor activity.

prepare the 2-chloro derivative of VP-16 (Scheme 27). Treatment of 4'-demethyl-1-O-(4,6-O-ethylidene-β-D-glucopyranosyl)-epipodophyllotoxin 24 (VP-16) with four equivalents of LDA at -78° in dry THF produced a pale yellow suspension. Excess hexachloroethane was added and the mixture warmed very slowly to room temperature and stirred for an additional 18h. Normal workup and PTLC (hexanes/ethyl acetate, 1:3) afforded 2-chloro-4'-O-demethyl-1-O-(4,6-O-ethylidene-β-glucopyranosyl)epipodophyllotoxin 150, albeit in only 10% yield. The remaining product was starting material. The low yield is believed to be due to the insolubility of the polyanion under the reaction conditions of -78° with THF as the solvent. The yield may be improved by the use of polar co-solvents such as HMPT. The 360 M Hz ^{1}H nmr spectrum and mass spectrum of 150 are shown in Figures 9 and 10.

Biological testing of derivative 150 against P388 Leukemia showed it to be as active as the current clinical agent, VP-16, having a T/C of greater than 500%. The results of further testing being conducted to determine whether it is in fact a more effective antitumour agent were not available at the time this thesis was written. The test results for compound 150 are in table 10.

In summary, we have found a very simple method for preparing nonenolisable podophyllotoxin derivatives which still contain the vitally important trans γ-lactone moiety. This route has led to the preparation of 2-chloro derivatives which have a high activity

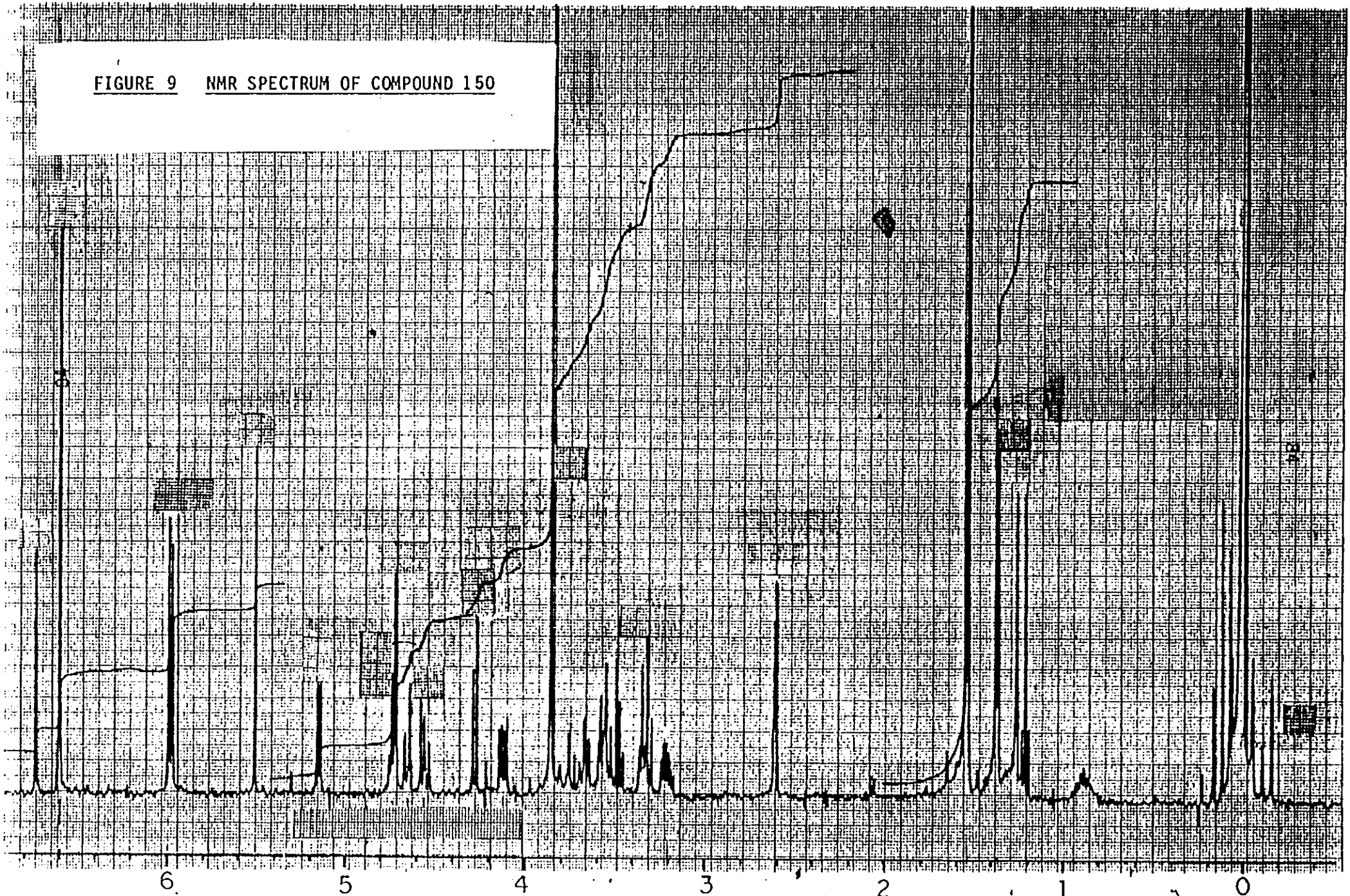


24

150

SCHEME 27

FIGURE 9 NMR SPECTRUM OF COMPOUND 150



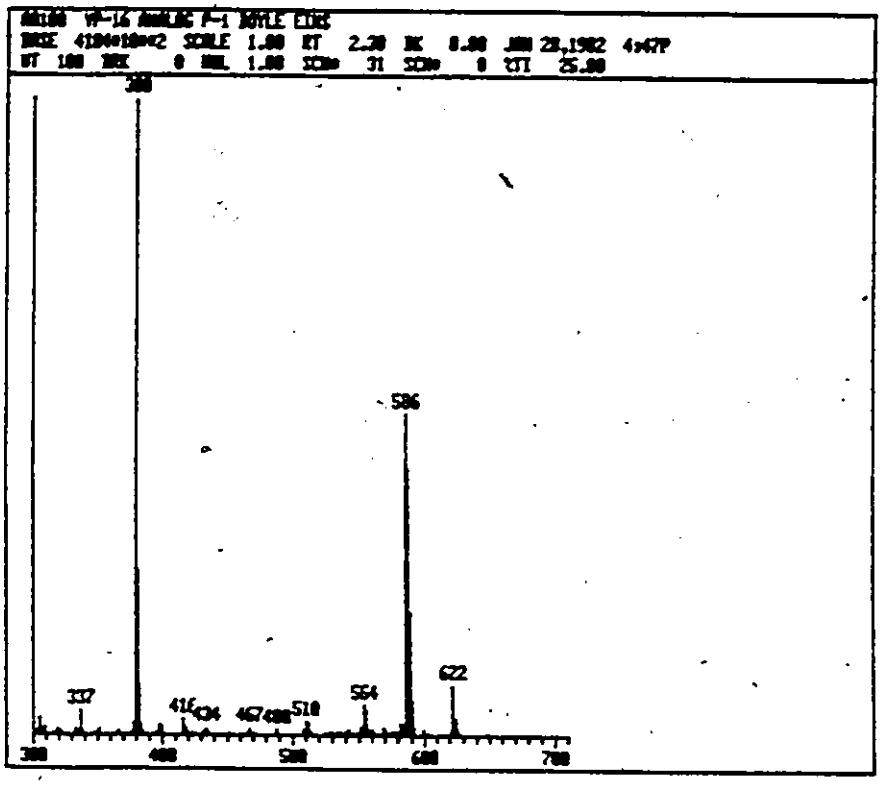
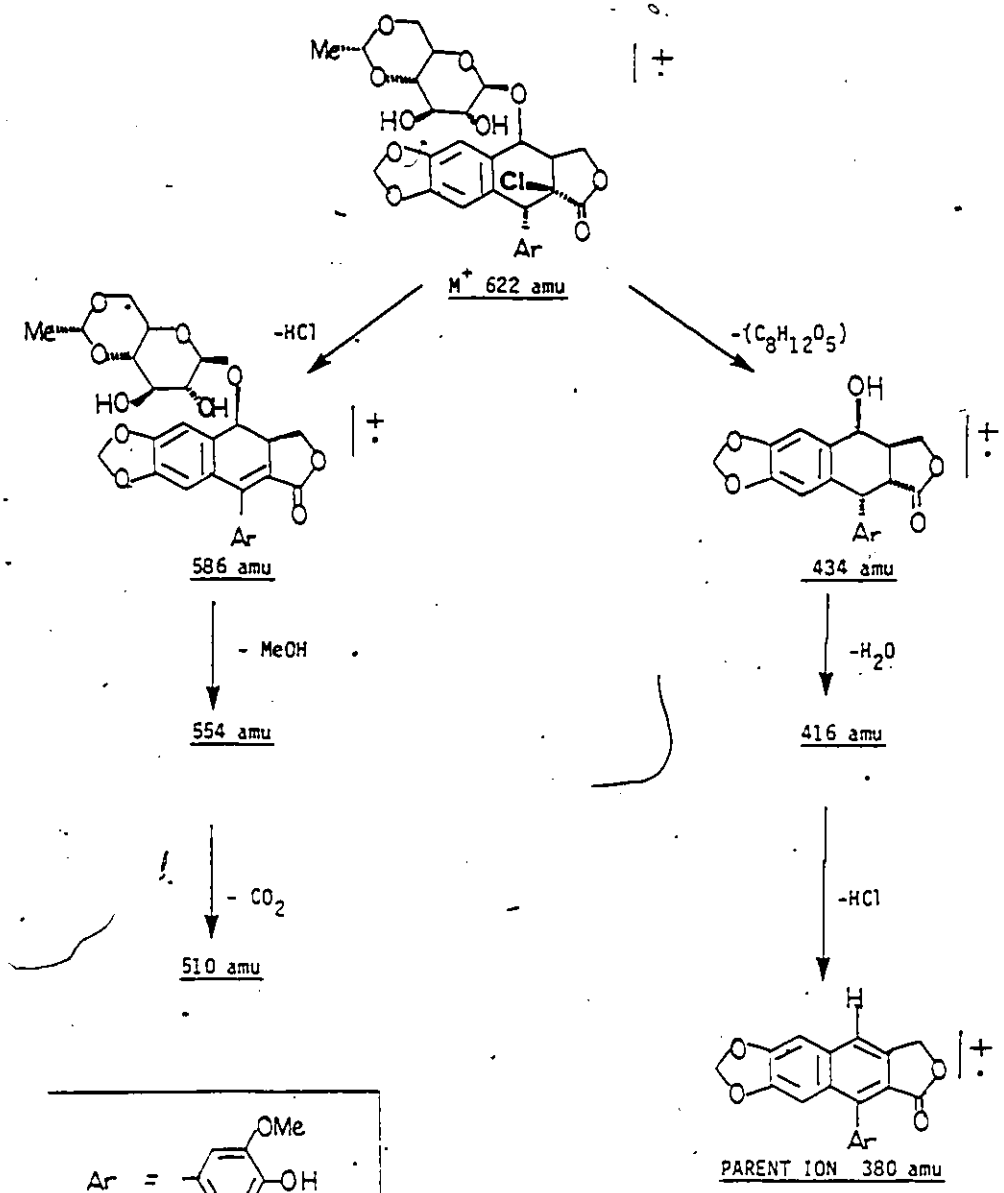


FIGURE 10 MASS SPECTRUM OF COMPOUND 150

PROPOSED M.S. FRAGMENTATION PATHWAY



in the Leukemia P388 tests. The most exciting results were obtained with the 2-chloro VP-16 derivative which may prove to be a better agent than VP-16 , the currently used clinical agent , when further studies into its effectiveness have been completed. This scheme could be used to introduce a wide variety of substituents at C_2 in both the podophyllotoxin and podophyllotoxin glycoside series..

Trust in the LORD with all thine heart;
and lean not unto thine own understanding.
In all thy ways acknowledge him,
and he shall direct thy paths.

PROVERBS 3:5,6

EXPERIMENTAL

GENERAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations are for chloroform solutions using a Perkin-Elmer 141 polarimeter. Infrared spectra were recorded on the Unicam SP1100 and the Beckman IR-20A spectrophotometers. Absorptions are reported in cm^{-1} and are noted as strong (s), medium (m), weak (w) or broadened (br). ^{1}H nmr spectra were obtained on Varian HA-100 and T-60 spectrometers. ^{13}C nmr spectra were obtained on a Varian FT-80 spectrometer. All spectra were taken using deuterochloroform ($CDCl_3$) as solvent (unless otherwise indicated) and tetramethylsilane (TMS) as the internal standard. The chemical shifts are relative to the internal standard, TMS. The coupling patterns are noted as singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublet (dd), doublet of triplets (dt), doublet of quartets (dq), broadened (br) or multiplet (m). Mass spectra were obtained on a AEIMS 9025 instrument .

Thin layer chromatography (TLC) was performed on Merck 60F 254 precoated silica plates of 0.25 mm thickness. Preparative thin layer chromatography (PTLC) was carried out on plates coated with a 0.5 mm layer of Kieselgel. Column chromatography was performed using silica gel (Baker 60-200 mesh) as the adsorbant. High performance liquid chromatography (HPLC) was carried out using PrepPak^{tm}-500/ silica

cartridges on a Waters 500 instrument. Microanalyses were carried out by Canadian Microanalytical Service Ltd, Vancouver, B.C.

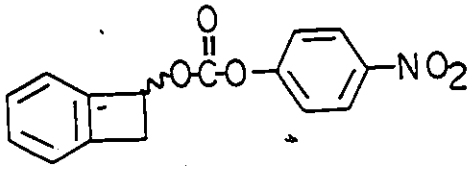
Tetrahydrofuran (THF) was always distilled over sodium/benzophenone under a nitrogen atmosphere immediately prior to use. All other solvents were distilled or of reagent grade quality.

Normal workup involved pouring the reaction mixture into water or saturated ammonium chloride solution, extracting three times with methylene chloride, drying the organic extracts with magnesium sulphate and evaporating the solvents on a rotary evaporator.

PART I (A)

Preparation of 92

NEt_3 (222 mg, 2.2 mmol) was added to a stirred solution of benzocyclobutenol 43 (252 mg, 2.0 mmol) and p-nitrophenylchloroformate (242 mg, 2.2 mmol) in anhydrous ether (10 ml) at room temperature. The mixture was stirred for 30 min. and then filtered to remove the precipitated $NEt_3 \cdot HCl$. Evaporation of the solvent followed by column chromatography (hexanes/ethyl acetate, 2:1) afforded 92 (500 mg, 85%) as a clear yellow oil.



$C_{15}H_{11}NO_4$
285.25

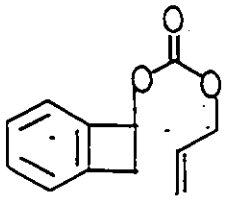
IR ($CHCl_3$) υ_{max} (cm^{-1}) 1780 (s), 1600 (s), 1530 (s), 1310 (s).

^1H nmr δ (ppm) 3.38 (dd, J=14.0, 1.5 Hz, 1H), 3.75 (dd, J=14.0, 4.0 Hz, 1H), 6.00 (dd, J=4.0, 1.5 Hz, 1H), 7.36 (m, 1H), 7.43 (d, J=10.0 Hz, 2H), 8.30 (d, J= 10.0 Hz, 2H).

Preparation of 88

Allyl alcohol (58 mg, 1.0 mmol) was dissolved in 0.5 ml dry THF and added slowly to a stirred solution of NaH (48 mg, 1.0 mmol) in THF (2.5 ml) at 0° C. Compound 92 (285 mg, 1.0 mmol) was added and the reaction mixture stirred for an additional 30 min. Normal workup followed by column chromatography (CH_2Cl_2) afforded the

carbonate, 88 (100 mg, 50%) as a colorless oil.



$C_{12}H_{12}O_3$
204.22

IR ($CHCl_3$) υ_{max} (cm^{-1}) 1780 (s), 1605 (s).

^1H nmr δ (ppm) 3.31 (dd, J=14.0, 1.5 Hz, 1H. 3.74 (dd, J=14.0, 4.0 Hz, 1H), 4.72 (m, 2H), 5.30 (m, 2H), 7.31 (m, 4H).

Attempted thermolysis of 88

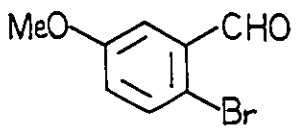
The carbonate, 88 (100 mg, 0.5 mmol) was dissolved in 3 ml o-dichlorobenzene, sealed in a thick walled glass tube and heated in an oven at 180° for 5h. The solution was cooled to rt. and the solvent evaporated. An nmr spectrum of the crude oil revealed it to be mainly unreacted starting material.

Preparation of 4-methoxybenzocyclobutenol 93

i. Preparation of 2-bromo-5-methoxybenzaldehyde :

m-Anisaldehyde (50.0g, 0.37 mol) and bromine (58 g, 0.37 mol) were dissolvedin 250 ml glacial acetic acid and left for 24 h. Water was added to precipitate the crude product which was collected by suction filtration and air dried. Recrystallization

from ether/hexanes yielded 2-bromo-5-methoxybenzaldehyde (64.0 g, 81%) as colorless plates.

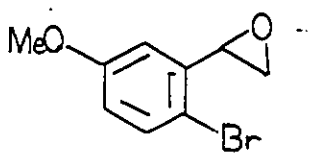


$C_8H_7O_2Br$
215.05

mp 73°C

ii. Preparation of 2-bromo-5-methoxystyrene oxide:

2-Bromo-5-methoxybenzaldehyde (15.0 g, 70 mmol), trimethylsulfonium chloride (10.5 g) and benzyltriethylammonium chloride (500 mg) were suspended in CH_2Cl_2 (100 ml). The solution was stirred and cooled in an ice-bath and 100 ml of 50% NaOH was added dropwise. After the addition was completed the reaction mixture was warmed to rt , stirred for a further 1 h , diluted with 50 ml of water and extracted three times with 25 ml of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, the solvent evaporated and the crude liquid was distilled under vacuum. The yield of 2-bromo-5-methoxystyrene oxide was 14.0 g (86%) of a colorless liquid.



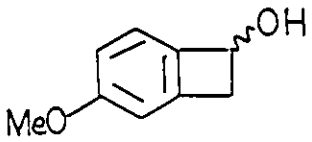
$C_9H_{12}O_2Br$
232.11

Bp 109° (1.5 mm)

^1H nmr δ (ppm) 2.83 (dd, J= 2.0, 6.0 Hz, 1H), 3.38 (dd, J=6.0, 4.0 Hz, 1H), 3.97 (s, 3H), 4.33 (dd, J=4.0, 2.0 Hz, 1H, 6.80-6.95 (m, 2H), 7.55 (dd, J=8.0 Hz, 1H).

iii. Preparation of 4-methoxybenzocyclobutenol

2-Bromo-5-methoxystyrene oxide (8.0 g, 35 mmol) and $MgBr_2$ (28 ml, 2.5 M in ether) were dissolved in 150 ml of dry THF. The solution was stirred and cooled to -78°C during which time the $MgBr_2$ precipitated. The reaction mixture was then treated with 16 ml of n-BuLi (hexane solution), kept at -78° for 30 minutes and then warmed slowly to rt. Addition of saturated NH_4Cl solution, followed by extraction once with ether and three times with CH_2Cl_2, drying of the combined organic extracts over $MgSO_4$ and evaporation of the solvents yielded a yellow oil. Chromatography on silica gel (HPLC), hexanes/ethyl acetate (4:1), afforded after recrystallization 3.76g (72%) 4-methoxybenzocyclobutenol as colorless needles.



$C_9H_{10}O_2$

150.17

Mp 39-42°C (ether/hexanes)

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300-3600 (br).

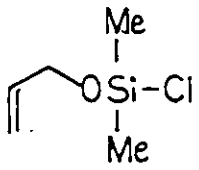
^1H nmr δ (ppm) 2.75 (1H, OH), 2.94 (dd, J=14.0, 1.0 Hz, 1H), 3.50 (dd, J=14.0, 4.5 Hz, 1H), 3.76 (s, 3H), 5.15 (dd, J=4.5, 1.0 Hz, 1H), 6.60-7.20 (m, 3H).

^{13}C nmr δ (ppm) 41.7, 55.4, 70.0, 108.9, 114.1, 123.6, 139.8, 143.4, 161.1.

Analysis Calculated for $C_9H_{10}O_2$: C, 71.98; H, 6.71.
Found C, 71.71; H, 6.58.

Preparation of 94

Allyl alcohol (2.90 g, 50 mmol) and pyridine (3.95 g, 50 mmol) were added slowly to a solution of freshly distilled dichlorodimethylsilane (12.91 g, 0.1 mol) in 50 ml of anhydrous ether at 0°C. Immediate precipitation of pyridinium hydrochloride occured and the mixture was stirred at 0° for approximately 1 h. The suspension was filtered and the ether evaporated. Distillation of the crude product afforded O-(chlorodimethylsilyl)allyl alcohol (3.60 g, 80%) as a colorless liquid.



$C_5H_{11}OSiCl$

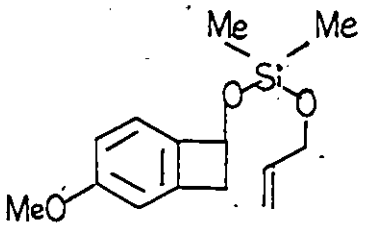
150.67

Bp 122-124°C

^1H nmr δ (ppm) 0.1 (s, 6H), 3.84 (m, 2H), 4.86 (m, 2H), 5.43 (m, 1H).

Preparation of 89

4-Methoxybenzocyclobutenol 93 (300 mg, 2.0 mmol) and pyridine (158 mg, 20 mmol) were added to a solution of 94 (150 mg, 2.0 mmol) in 10 ml of anhydrous ether at 0°C. The solution was stirred for 1 h and filtered to remove the pyridinium hydrochloride. The solution was dried and the solvent evaporated to afford a yellow oil. Purification by HPLC (hexanes/ethyl acetate, 20:1) furnished 89 (266 mg, 51%) as a colorless oil.



$C_{14}H_{20}O_3Si$

264.37

^1H nmr δ (ppm) 0.10 (s, 6H), 2.95 (dd, J=14.0, 1.5 Hz, 1H), 3.48 (dd, J=14.0, 4.0 Hz, 1H), 3.78 (s, 3H), 4.13 (m, 2H), 4.90-5.40 (complex m, 3H), 5.84 (m, 1H, 6.70 (d, J=2.0 Hz, 1H), 6.75 (dd, J=8.0, 2.0 Hz, 1H), 7.11 (d, J=8.0 Hz, 1H).

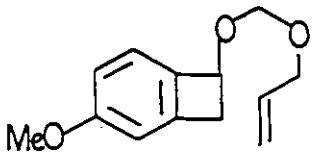
Attempted thermolysis of 89

The dialkoxysilane derivative 89 (106 mg, 0.4 mmol) was refluxed in 2.0 ml of toluene for 24 h. Evaporation of the solvent afforded a yellow oil. TLC showed the presence of at least five products and the nmr spectrum of the crude product revealed the loss of the silicon moiety by the absence of the 6H singlet upfield at approximately 0.1 ppm. No attempt was made to isolate or identify the products.

Preparation of 90

4-Methoxybenzocyclobutenol (300 mg, 2.0 mmol) and 1-chloro-methoxyprop-2-ene 95 (212 mg, 2.0 mmol) were dissolved in 10 ml of anhydrous ether. Triethylamine (202 mg) was added and the contents were stirred overnight. The solution was washed with water and then 5% HCl, dried and the solvent evaporated. A yellow oil was obtained which was subjected to column chromato-

graphy (hexanes/ethyl acetate, 3:1) furnishing 90 (220 mg, 50%) as a colorless oil.



$C_{13}H_{16}O_3$
220.26

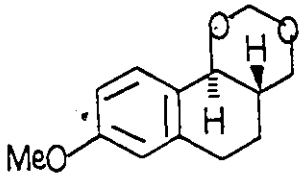
IR ($CHCl_3$) υ_{max} (cm^{-1}) 1610 (s).

^1H nmr δ (ppm) 3.10 (dd, J=14.0, 1.5 Hz, 1H), 3.48 (dd, J=14.0, 4.0 Hz, 1H), 3.78 (s, 3H), 4.15 (dd, J=6.0, 1.0 Hz, 1H), 4.90 (s, 2H), 5.07-5.41 (m, 3H), 5.95 (m, 1H), 6.70 (d, J=2.0 Hz, 1H), 6.75 (dd, J=8.0, 2.0 Hz, 1H), 7.11 (d, J=8.0 Hz, 1H).

Thermolysis of 90

Compound 90 (116 mg) was refluxed in 10 ml of toluene containing K_2CO_3 (50 mg) for 24 h. The solution was filtered and the solvent evaporated affording a white solid. Recrystallization from ether/hexanes furnished 102 mg (86%) of the tricyclic adduct 96 as colorless plates.

$C_{13}H_{16}O_3$
220.26
Mp 76-77°C



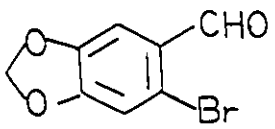
^{1}H nmr δ (ppm) 1.36-1.88(m, 2H), 2.04 (m, 1H), 2.82 (m, 1H), 3.51 (t, J=11.0 Hz, 1H), 3,80 (s, 3H), 4.13 (dd, J=11.0, 4.0 Hz, 1H), 4.34 (d, J=9.0 Hz, 1H), 4.93 (d, J=6.0 Hz, 1H), 5.38 (d, J=6.0 Hz, 1H), 6.62(d, J=2.0 Hz, 1H), 6.76 (dd, J=6.0, 2.0 Hz, 1H), 7.16 (d, J=8.0 Hz, 1H).

Analysis Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32.

Found : C, 70.94; H, 7.30.

Preparation of 2-bromo-4,5-(methylenedioxy)benzaldehyde 99

Piperonal, 98 was brominated according to Orr et al.[62] Treatment of 15.0 g (0.1 mol) of piperonal with 15.8 g of bromine in glacial acetic acid afforded after 24 h a crude solid after precipitation with water and filtration. Recrystallization from CH_2Cl_2/hexanes yielded 16.0g (70%) of 99 as long colorless needles.



$C_8H_5O_3Br$

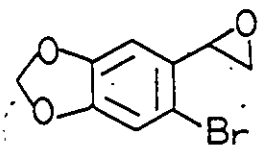
229.04

Mp 110°C (lit.mp. 111°)[62]

^{1}H nmr δ (ppm) 6.15 (s, 2H), 7.12 (s, 1H), 7.21 (s, 1H), 10.54 (s, 1H).

Preparation of 2-bromo-4,5-(methylenedioxy)styrene oxide 100

Treatment of 360 mg (1.5 mmol) of 2-bromo-4,5-(methylenedioxy)-benzaldehyde with 125 mg (1.6 mmol) of trimethylsulfonium chloride under the usual phase transfer conditions gave 317 mg (82%) of 2-bromo-4,5-(methylenedioxy)styrene oxide as colorless prisms after recrystallization from ether/hexanes.



$C_9H_7O_3Br$

243.06

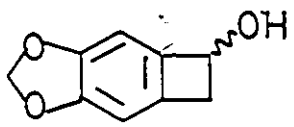
Mp 91°C

^{1}H nmr δ (ppm) 2.52(dd, J=6.0, 2.0 Hz, 1H), 3.05 (dd, J=6.0, 4.0 Hz, 1H), 4.05 (dd, J=4.0, 2.0 Hz, 1H), 5.90 (s, 2H), 6.60 (s, 1H), 6.85 (s, 1H).

M.S. m/e 243 (M^+), 245 (M+2).

Preparation of 4,5-(methylenedioxy)benzocyclobutenol 97

2-Bromo-4,5-(methylenedioxy)styrene oxide (200 mg, 0.8 mmol) in 10 ml of anhydrous ether at -78°C was treated first with 0.9 mmol of n-BuLi and then 1.6 mmol of $MgBr_2$ (ether solution). The reaction mixture was warmed to rt and worked up in the usual manner. The crude product was purified by column chromatography (hexanes/ethyl acetate, 4:1). The yield of 97 (colorless needles) after recrystallization from ether/hexanes was 101 mg (75%).



$C_9H_8O_3$

164.15

Mp 118-120°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3200-3550 (br).

^1H nmr δ (ppm) 2.23 (br, OH), 2.83 (dd, J=14.0, 1.0 Hz, 1H), 3.41 (dd, J=14.0, 4.5 Hz, 1H), 5.10 (dd, J=4.5, 1.0 Hz, 1H), 5.87 (s,,2H), 6.61 (s, 1H), 6.71 (s, 1H).

M.S. m/e 164 (M^+)

Analysis Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91.
Found: C, 65.49; H, 4.89.

Preparation of methyl-O-chloromethyl-4-hydroxybut-2-enoate 101

i. Preparation of methyl crotonate

Crotonic acid (43.0 g) and pTsOH (500 mg) were dissolved in 200 ml of absolute methanol and refluxed overnight. Most of the methanol was removed under vacuum and the remaining liquid was diluted with CH_2Cl_2 and washed several times with sat. $NaHCO_3$ solution. The organic phase was dried and the solvent removed. The crude ester was distilled at atmospheric pressure to yield 40 g (80%) of the pure ester as a colorless liquid.

Bp 106°C

^{1}H nmr δ (ppm) 2.00 (dd, J=7.0, 1.0 Hz, 1H), 3.83 (s, 3H), 5.98 (dqt, J=16.0, 1.0 Hz, 1H), 7.00 (dqt, J=16.0, 7.0 Hz, 1H).

ii. Preparation of methyl 4-bromocrotonate

Methyl crotonate (18.8 g) and NBS (33.4 g) were dissolved in 200 ml of CCl_4 and heated overnight. Filtration to remove the succinamide and evaporation of the solvent yielded a yellow liquid which was distilled under vacuum. Methyl 4-bromocrotonate (31.0 g) was obtained as a colorless liquid.

Bp 110°C (0.2 mm)

^{1}H nmr δ (ppm) 3.70 (s, 3H), 3.98 (ss, J=7.0, 1.0 Hz, 1H), 6.02 (dt, J=16.0, 1.0 Hz, 1H), 7.00 (dt, J=16.0, 7.0 Hz, 1H).

iii. Preparation of methyl 4-hydroxycrotonate

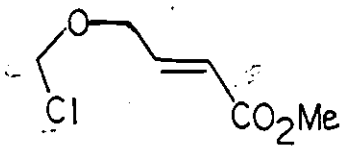
Methyl 4-bromocrotonate (17.9 g, 0.1 mol) and freshly prepared silver oxide (11.6 g) were suspended in 150 ml of distilled water and stirred at rt for 24 h. The contents of the flask were refluxed for 5 h and then filtered by suction. The water was evaporated and the crude yellow liquid distilled under vacuum. The product was obtained as a colorless liquid (5.35 g, 54%).

Bp 70°C (0.1 mm)

^{1}H nmr δ (ppm) 2.97 (br, OH), 3.77 (s, 3H), 4.30 (dd, J=4.0, 1.0 Hz, 2H), 6.07 (dt, J=16.0, 1.0 Hz, 1H), 7.03 (dt, J=16.0, 4.0 Hz, 1H).

iv. Preparation of 101

Methyl 4-hydroxycrotonate (1.0 g, .01 mol) and paraformaldehyde (0.475 g) were placed in a flask containing 10 ml of dry CH_2Cl_2. The flask was cooled to -20°C and HCl(g) was bubbled through the solution until all the paraformaldehyde was hydrolyzed. The reaction was stirred for 30 minutes and warmed to rt. Nitrogen gas was bubbled through the solution to remove any excess HCl (g) and then $MgSO_4$ was added to dry the solution. The solution was filtered and the solvents evaporated to afford a colorless oil which was used without further purification. This material was stored in the freezer and was normally used shortly after preparation since decomposition occurs readily to give the chloride derivative.



$C_6H_9ClO_3$

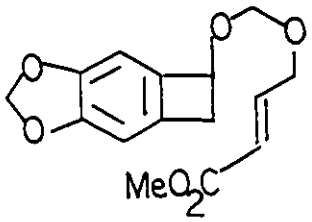
164.59

^1H nmr δ (ppm) 3.72 (s, 3H), 4.32 (dd, J=4.0, 1.0 Hz, 2H), 5.45 (s, 2H), 6.00 (dt, J=16.0, 1.0 Hz, 1H), 6.90 (dt, J=16.0, 4.0 Hz, 1H).

Preparation of compound 103

4,5-(Methylenedioxy)benzocyclobutenol (410 mg, 2.5 mmol) and 101 (375 mg, 2.5 mmol) were dissolved in anhydrous ether (20 ml).

Triethylamine (252 mg, 2.5 mmol) was added and the contents were stirred for 18 h. The reaction mixture was washed with water and then 5% HCl, dried and the solvent evaporated. The crude oil was purified by PTLC using hexanes/ethylacetate, 1:1 as the developer. The acetal 103 was obtained as a clear, colorless oil in 60% yield (438 mg).



$C_{15}H_{16}O_6$

292.18

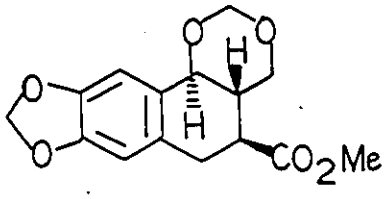
IR ($CHCl_3$) υ_{max} (cm^{-1}) 1730 (s), 1610 (s).

^1H nmr δ (ppm) 2.92 (dd, J=14.0, 1.0 Hz, 1H), 3.38 (dd, J=14.0, 4.5 Hz, 1H), 3.74 (s. 3H), 4.25 (dd, J=7.0, 2.0 Hz, 2H), 4.86 (s, 2H), 4.98 (dd, J=4.5, 1.0 Hz, 1H), 5.87 (s. 2H), 6.06 (dt, J=16.0, 2.0 Hz, 1H), 6.62 (s, 1H), 6.70 (s, 1H), 7.00 (dt, J=16.0, 7.0 Hz, 1H).

Thermolysis of 103

The benzocyclobutenol derivative 103 (100 mg, 0.34 mmol) was refluxed in 10 ml of toluene containing 50 mg K_2CO_3 or a period of 48 h. The solution was filtered and the solvent evaporated yielding a solid product that was purified by PTLC (hexanes/ethyl acetate,

2:1). Recrystallization from CH_2Cl_2/hexanes afforded the tetracyclic adduct 104 (75 mg, 75%) as small colorless needles.



$C_{14}H_{16}O_6$

292.18

Mp 155°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 1730 (s), 1610 (s).

^1H nmr δ (ppm) 2.18 (qd, J=11.6, 4.0 Hz, 1H), 2.59 (td, J=11.6, 6.1 Hz, 1H), 2.92 (dd, J=11.6, 6.1 Hz, 1H), 3.09 (dd, J=10.4, 11.6 Hz, 1H), 3.56 (t, J=10.8 Hz, 1H), 3.73 (s, 3H), 4.19 (dd, J=4.0, 11.0 Hz, 1H), 4.35 (d, J=10.0 Hz, 1H), 4.90 (d, J=6.2 Hz, 1H), 5.26 (d, J=6.2 Hz, 1H), 5.92 (s, 2H), 6.55 (s, 1H), 6.94 (s, 1H).

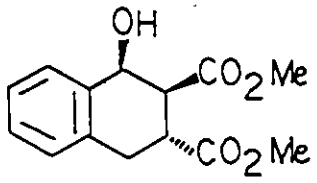
M.S. m/e 292 (M^+)

Analysis Calcd. for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52.
Found : C, 61.77; H, 5.55.

PART I (B)

Photolysis of o-tolualdehyde in the presence of dimethyl fumarate

A solution of o-tolualdehyde 53 (12.0 g, 0.1 mol) and dimethyl fumarate (14.2 g, 0.1 mol) in dry acetone (300 ml) was irradiated for 12 h in a quartz apparatus with a medium pressure mercury arc (450 W, Hanovia Reading Reactor) at room temperature while oxygen-free nitrogen was bubbled through the solution. The acetone was evaporated and the crude oil was purified by HPLC (hexanes/ethyl acetate; 3:1) affording the photoadduct 116 (21.0 g, 78%) as a pale yellow viscous oil.



$C_{14}H_{22}O_5$

264.32

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300-3550 (br), 1720 (s)

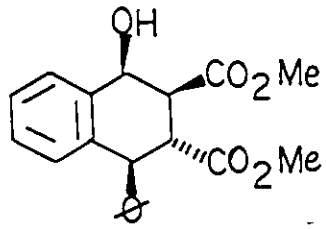
^1H nmr δ (ppm) 2.80-3.40 (m, 4H), 2.55 (b, OH), 3.94 (s, 6H), 5.06 (d, J=3.0 Hz, 1H), 7.02-7.20 (m, 4H).

^{13}C nmr δ (ppm) 32.06, 36.87, 48.08, 52.15, 68.04, 126.92, 128.67, 129.71, 133.79, 135.92, 172.95, 175.45.

Photolysis of o-benzylbenzaldehyde in the presence of dimethyl fumarate

o-Benzylbenzaldehyde, 115, was obtained by PCC oxidation of o-benzylbenzyl alcohol in 98 % yield. A solution of 115 (8.0 g, 41 mmol) and dimethyl fumarate (5.88g, 41 mmol) in dry acetone (200 ml) was irradiated for 8 h in a quartz apparatus as detailed

in the preceding procedure. The acetone was evaporated and the crude oil was purified by HPLC (hexanes/ethyl acetate; 5:1). Compound 117 was obtained after recrystallization from ether/ petroleum ether as colorless prisms in 51 % yield (7.13 g).



$C_{20}H_{20}O_5$

340.36

Mp 149-150°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300- 3550 (br), 1730 (s), 1600 (w).

^1H nmr δ (ppm) 2.70 (d, J=3.0 Hz, 1H), 3.26 (dd, J=3.0, 11.0 Hz, 1H), 3.61 (d, J=11.0 Hz, 1H), 4.20 (d, J=11.0 Hz, 1H), 5.20 (t, J=3.0 Hz, 1H), 6.76 (m, 1H), 7.20 (m, 8H).

^{13}C nmr δ (ppm) 45.63, 48.58, 49.69, 51.64, 52.27, 68.10, 126.93, 127.12, 128.56, 128.81, 129.19, 129.57, 135.92, 138.16, 142.81, 172.73, 175.08.

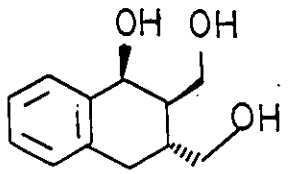
M.S. m/e 340 (M^+).

Analysis Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92.
Found: C, 70.34; H, 6.13.

Reduction of 116 to the triol 118

The diester 116 (13.50 g, 50 mmol) was dissolved in dry THF (25 ml) and added dropwise to a suspension of LAH (5.34 g) in 225 ml of THF. The solution was refluxed overnight and worked up

in the usual manner affording a solid crude product. Chromatography (hexanes/ethyl acetate; 1:4) furnished a polar compound which was recrystallized from methanol/ether and was identified to be the triol 118. The yield of 118 as colorless needles was 8.50 g (79%).



$C_{12}H_{16}O_3$

208.25

Mp 96-98°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3350- 3550 (br)

^1H nmr δ (ppm) 1.76 (m, 1H), 2.16(m, 1H), 2.50-2.97 (m, 2H), 3.63 (d, J=5.0 Hz, 1H), 4.30-4.80 (m, 3H, exchanged with D_2O), 4.78 (d, J=3.0 Hz, 1H), 6.95-7.15 (m, 4H).

^{13}C nmr δ (ppm) 32.04, 33.76, 43.30, 62.93, 64.16, 69.89, 125.57, 127.19, 128.31, 128.66, 136.52, 138.91.

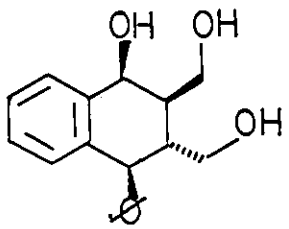
M.S. m/e 208 (M^+)

Analysis Calcd. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.75.
Found: C, 68.72; H, 7.86.

Reduction of 117 to the triol 119

The diester 117 (6.80 g, 20 mmol) was reduced with LAH (840 mg) in dry THF (150 ml). The solution was refluxed overnight. Normal

workup, followed by recrystallization of the crude solid from ether/hexanes gave colorless prisms of the triol 119 , 4.08 g (80%).



$C_{18}H_{20}O_3$

284.34

Mp 134-135°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3350-3550 (br), 1600 (w).

^1H nmr δ (ppm) 1.92-2.56 (m, 2H), 3.26-3.84 (m, 2H), 3.88-4.22 (m, 5H), 4.52 (t, J=5.0 Hz, 1H), 4.91 (d, J=3.0 Hz, 1H), 4.88 (s, 1H), 6.68 (m, 1H), 6.96-7.36 (m, 8H).

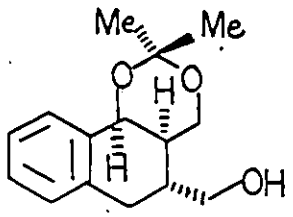
^{13}C nmr δ (ppm) 40.57, 42.53, 47.50, 60.25, 64.02, 71.14 125.62, 126.12, 127.53, 128.21, 128.91, 129.75, 129.92, 138.51, 140.53, 145.69.

Analysis Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09.
Found: C, 75.76; H, 7.51.

Preparation of the ketal derivative 120

The triol, 118 (5.60 g, 27 mmol) and $ZnCl_2$ (5.60 g) were added to 50 ml of acetone and stirred at rt for 24 h. The solution was diluted with water and CH_2Cl_2 and the phases were separated. The aqueous phase was extracted three times with CH_2Cl_2 and the combined organic extracts were dried and the solvents evaporated leaving a

white solid. Chromatography (ethyl acetate/hexanes; 2:1) furnished 5.31 g (79%) of the ketal 120 after recrystallization from ether/ petroleum ether as colorless needles. A small amount of a faster moving product on tlc was obtained in 16% yield . This product was tentatively assigned the structure of the seven-membered cyclic ketal 124 , based on the nmr spectrum.



120

$C_{15}H_{20}O_3$

248.31

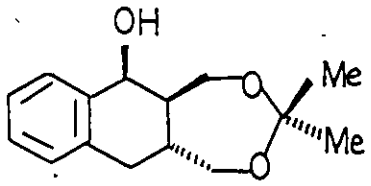
Mp 111-113°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3350-3550 (br).

^1H nmr δ (ppm) 1.37 (s, 6H), 2.30-3.05 (m, 4H), 3.37-4.30 (m, 5H), 4.98 (d, J=3.0 Hz, 1H), 7.15 (m, 4H).

Analysis Calcd. for $C_{15}H_{20}O_3$: C, 72.55, H, 8.12.

Found : C, 72.09, H, 8.49.



124

$C_{15}H_{20}O_3$

248.31

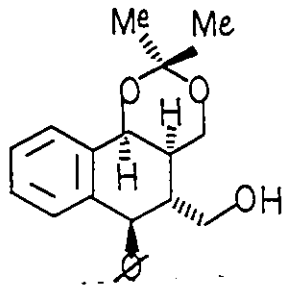
Mp 145-146°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3350-3550 (br).

^1H nmr δ (ppm) 1.35 (s, 6H), 1.53-2.90 (m, 5H), 3.55-4.30 (m, 4H), 4.65 (d, J=3.0 Hz, 1H), 7.20 (m, 4H).

Preparation of the ketal derivative 121

The triol 119 (3.0 g, 10.6 mmol) and $ZnCl_2$ (1.10 g) were added to 25 ml of dry acetone and the mixture was stirred for 24 h. Workup in the usual manner afforded a white solid which was recrystallized from ether/hexanes to give 2.30 g (77%) of the isopropylidene derivative 121, colorless needles.



$C_{21}H_{24}O_3$

324.40

Mp 155.5-156.5°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300-3500 (br), 1600 (w).

^1H nmr δ (ppm) 1.34 (s, 6H), 1.90 (m, 2H), 2.41 (qd, J=10.0, 4.0 Hz, 1H), 3.30-4.24 (m, 4H), 4.70 (d, J=2.0 Hz, 1H), 6.70 (m, 1H), 7.02-7.36 (m, 8H).

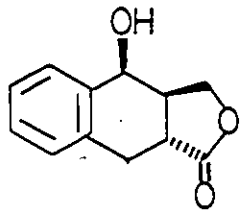
^{13}C nmr δ (ppm) 24.81, 41.17, 46.30, 49.10, 63.98, 64.52, 69.89, 101.09, 126.58, 126.71, 128.61, 129.35, 130.35, 138.20, 140.09, 144.19.

Analysis Calcd. for $C_{21}H_{24}O_3$: C, 77.45; H, 7.46.
Found : C, 76.74; H, 7.32.

Oxidation of 120 to form the lactone derivative 122

The isopropylidene derivative 120 (156 mg, 0.6 mmol) was dissolved in dry CH_2Cl_2 and added to a stirring mixture of $KMnO_4$

(97 mg, 0,6 mmol) and ϕCH_2NEt_3Cl (137 mg, 0.6 mmol) in 5 ml of dry CH_2Cl_2. The solution was stirred for 18 h at which time the reaction mixture was filtered to remove the precipitated MnO_2. The solution was acidified with 5% HCl and then extracted three times with CH_2Cl_2. The combined organic extracts were dried and the solvent evaporated. The crude product was purified by PTLC (ethyl acetate) affording the lactone derivative 122 (75 mg, 62%) as colorless prisms after recrystallization from ether/ hexanes.



$C_{12}H_{12}O_3$

204.22

Mp 168°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300-3550 (br), 1775 (s).

^1H nmr δ (ppm) 2.48-3.40 (m, 4H), 3.50 (complex m, 2H), 4.91 (d, J=3.0 Hz, 1H), 4.50 (br, OH), 7.24-7.70 (m, 4H).

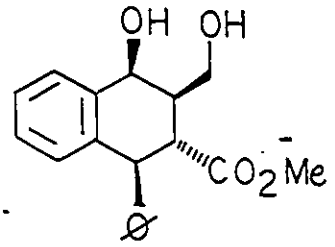
M.S. m/e 204 (M^+).

Analysis Calcd. for $C_{12}H_{12}O_3$: C, 69.57; H, 5.93.
Found : C, 69.51; H, 5.94.

Reduction of the diester 117 with $LiEt_3BH$

The diester 117 (170 mg, 0.5 mmol) was dissolved in 5 ml of dry THF and cooled to -78°C under a N_2 atmosphere. $LiEt_3BH$ (1.5 ml, 1M in THF) was added slowly by a syringe and the solution was

stirred for 2 h at -78° and at rt for an additional 18 h. Addition of 5 ml of 5% aqueous HCl, followed by extraction once with ether and three times with CH_2Cl_2 yielded a crude solid product. Purification by PTLC (CH_2Cl_2/ether; 1:1) afforded the diol ester, 125 (120 mg, 75%) as colorless needles.



$C_{19}H_{20}O_4$

312.35

Mp 95°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300- 3550 (br), 1730 (s), 1600 (w)

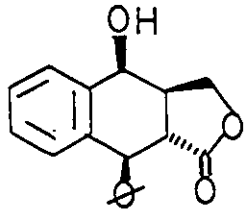
^1H nmr δ (ppm) 1.00 (br, 2 OH), 2.53 (dd, J= 11.0, 4.0 Hz, 1H), 3.08 (t, J= 11.0 Hz, 1H), 3.50 (s, 3H), 3.76 (d, J=11.0 Hz, 1H), 4.24 (m, 2H), 5.13 (d, J=4.0 Hz, 1H), 6174 (d, J=8.0 Hz, 1H), 7.02-7.48 (m, 8H).

Analysis Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45.
Found : C, 73.19; H, 6.43.

Preparation of the lactone 123 from 125

The diol ester (72 mg, 0.23 mmol) , CH_3SO_3H (0.1 ml) and water (0.5 ml) were refluxed overnight in 2.5 ml of acetone. The solvents were removed on the rotary evaporator and the residue was dissolved in CH_2Cl_2, washed with 10% aqueous $NaHCO_3$, dried and the solvent evaporated. Recrystallization of the crude product from CH_2Cl_2/hexanes afforded the lactone 123 (45 mg, 70 %) as

colorless plates.



$C_{18}H_{16}O_3$

280.31

Mp 193°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300- 3550 (br), 1775 (s), 1600 (w).

^1H nmr δ(ppm) 2.44 (br, OH), 2.49-2.87 (m, 1H), 3.33 (dd, J=11.2, 14.0 Hz, 1H), 4.16 (d, J=11.2 Hz, 1H), 4.45 (dd, J=14.0, 8.4 Hz, 1H), 4.86 (d, J=2.8 Hz, 1H), 6.80 (m, 1H), 6.97- 7.39 (m, 7H), 7.68 (dd, J=7.5, 3.0 Hz, 1H).

M.S. m/e 280 (M^+), 262 ($M-H_2O$), 217 ($262-CO_2$), 202 ($M-C_6H_6$).

Analysis Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75.

Found: C, 77.47; H, 5.67.

Preparation of 6-(3',4',5'-trimethoxybenzyl)piperonal 109

Procedure A

6-Bromopiperonal dimethyl acetal 126 (278 mg, 1 mmol) was dissolved in 1 ml of dry THF and cooled to -78° under a N_2 atmosphere. n-BuLi (0.42 ml, 1.1 mmol, 2.4 M in hexanes) was added by syringe and the solution was stirred for 10 minutes. n-Bu_3PCuI (196 mg, 0.5 mmol) was added in a small volume of THF followed by 1-bromomethyl-3,4,5-trimethoxybenzene (≈130 mg, 0.5 mmol) and the reaction mixture was stirred for 1 h at -78° and then warmed to rt. The reaction was worked up after a total reaction time of 18 h in the usual manner. Column chromatography (hexanes/ethyl acetate; 3:1) afforded 178 mg of the desired aldehyde dimethyl acetal , 127, as a colorless oil.

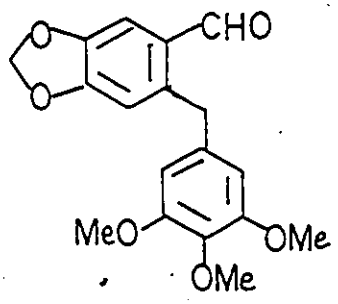
$C_{20}H_{22}O_7$

374.38

^1H nmr δ (ppm) 3.27 (s, 3H), 3.80 (s, 9H), 3.93 (s, 2H), 5.88 (s, 2H), 5.90 (s, 1H), 6.35 (s, 2H), 6.45 (s, 1H), 7.07 (s, 1H).

The coupling product, 127 was dissolved in 10 ml of methanol and 1 ml of 5% aqueous HCl was added. Almost immediately the desired aldehyde crystallized out of solution. Filtration and recrystallization from ether/hexanes afforded 6-bromo-(3',4',5'-tri-

methoxybenzyl)piperonal, 109 (140 mg., 84% overall) as fine colorless needles.



$C_{18}H_{18}O_6$

330.32

Mp 123°C (Lit.mp. 124-125°)

IR ($CHCl_3$) υ_{max} (cm^{-1}) 1690 (s), 1600 (s).

^1H nmr δ (ppm) 3.84 (s, 6H), 3.86 (s, 3H), 4.34 (s, 2H), 6.08 (s, 2H), 6.38 (s, 2H), 6.72 (s, 1H), 7.36 (s, 1H), 9.93 (s, 1H).

^{13}C nmr δ (ppm) 37.74, 56.12, 60.84, 102.07, 105.73, 109.01, 111.04, 128.57, 135.89, 136.67, 140.35, 147.07, 152.56, 153.44, 189.62.

M.S. m/e 329 (M^+-1).

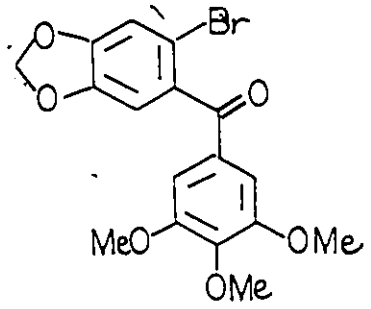
Procedure B

i. Preparation of 1-bromo-4,5-(methylenedioxy)-2-(3',4',5'-trimethoxybenzoyl)benzene 130 :

1-Iodo-3,4,5-trimethoxybenzene, 128 (5g, 17 mmol) was dissolved in 20 ml of dry THF and cooled to -78°C , under a N_2 atmosphere. The addition of n-BuLi (7.79 ml, 1.1 equiv.) resulted in the formation of a deep red solution. After 10 minutes, 6-bromopiperonal, 99 was added and the solution was stirred for 30 minutes at -78° and then

warmed to rt. The solution was stirred overnight and worked up in the normal manner. The crude product, a orange oil (6.0 g) was oxidized without further purification.

The benzhydrol 129 (6.0 g, 15.2 mmol) was dissolved in dry CH_2Cl_2 and added slowly to a cooled (0°C) suspension of PCC (4.9 g, 22.8 mmol) in 100 ml of dry CH_2Cl_2. The reaction mixture was stirred for approximately 4 h and then filtered through a short fluorisil column to remove chromium salts. The solvent was evaporated and the crude solid was recrystallized from ether (hot/cold) affording 5.1 g (85%) of 1-bromo-4,5-(methylenedioxy)-2-(3',4',5'-trimethoxybenzoyl)benzene as colorless plates.



$C_{17}H_{15}O_6Br$

395.21

Mp 150°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 1670 (s), 1590 (s).

^1H nmr δ (ppm) 3.87 (s, 6H), 3.94 (s, 3H), 6.06 (s, 2H), 6.82 (s, 1H), 7.07 (s, 1H).

^{13}C nmr δ (ppm) 56.34, 60.97, 102.37, 107.79, 109.10, 111.34, 113.31, 131.32, 133.59, 143.23, 147.27, 49.71, 153.09.

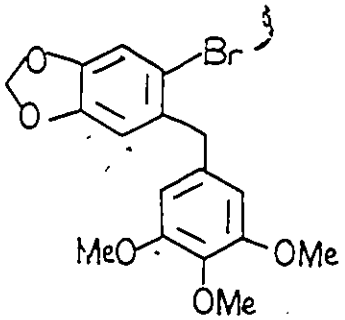
M.S. m/e 394 (M^+), 396 (M+2).

Analysis Calcd. for $C_{17}H_{15}O_6Br$: C, 51.66; H, 3.83.
Found : C, 51.44; H, 3.79.

ii. Preparation of 1-bromo-4,5-(methylenedioxy)-2-(3',4',5'-trimethoxybenzyl)benzene 131

The ketone (5g) was treated with activated zinc (10.0 g) in a mixture of concentrated HCl (28 ml), water (28 ml) and toluene (28 ml). HCl gas was bubbled through the reaction mixture for approximately 8 h. Workup consisted of dilution with water and ether and washing of the organic phase with a saturated $NaHCO_3$ solution. The organic phase was dried and the solvents evaporated leaving a yellow foam which was chromatographed (hexanes/ethyl acetate; 4:1) furnishing 131 (3.70 g, 77%) as colorless needles after recrystallization from ether / hexanes.

An alternate procedure involved the use of LAH / $AlCl_3$ as the reducing agent. The ketone 130 (5.0 g) was dissolved in a small volume of dry THF and added dropwise to a stirred suspension of LAH (963 mg, 25.4 mmol) and $AlCl_3$ (3.46 g, 25.4 mmol) in 100 ml of dry THF. When addition was complete the mixture was refluxed for 24 h. The excess reducing agent was destroyed with water and the layers separated. The organic phase was dried and the solvents evaporated affording 131 (4.46 g, 86%) as colorless needles after recrystallization from ether/hexanes.



$C_{17}H_{17}O_5Br$

381.23

Mp 121-121.5°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 1600 (s), 1130 (s), 1230 (s).

^{1}H nmr	δ (ppm) 3.83 (s, 9H), 3.94 (s, 2H), 5.92 (s, 2H), 6.40 (s, 2H), 6.60 (s, 1H), 7.00 (s, 1H).
^{13}C nmr	δ (ppm) 41.79, 56.10, 60.87, 101.66, 105.95, 110.39, 112.64, 114.64, 133.39, 135.34, 146.91, 147.46, 153.31.
M.S.	m/e 380 (M^+), 382 (M+2).

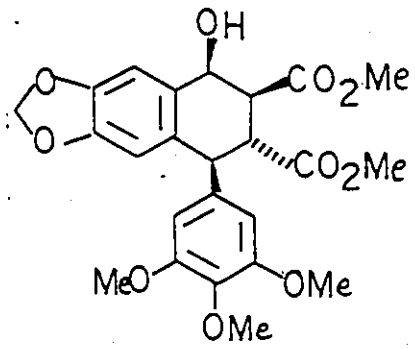
iii. Préparation of 6-(3',4',5'-trimethoxybenzyl)piperonal 109

The aryl bromide , 131 (2.0 g, 5.26 mmol) was dissolved in 20 ml of dry THF and cooled to -78°C under a N_2 atmosphere. n-BuLi (2.19 ml, 5.26 mmol) was added via syringe and the solution turned a deep orange color. The solution was stirred at -78° for 10 min. and then dry DMF (2.0 ml) was added . The solution turned a light shade of yellow and was warmed slowly to rt. and stirred for an additional 18 h. Normal workup afforded a crude solid product that was recrystallized from CH_2Cl_2 / hexanes , affording the desired aldehyde 109 (1.39 g, 80%) . This product was identical in all respects to the product obtained by procedure A.

Preparation of epiisopodophyllotoxin

Photolysis of aldehyde 109 in the presence of dimethyl fumarate

A solution of 6-(3',4',5'-trimethoxybenzyl)piperonal , 109 (660 mg, 2.0 mmol) and dimethyl fumarate (288 mg, 2.0 mmol) in dry THF (100 ml) was irradiated for 18 h in a quartz apparatus with a long uv. lamp (λ_{max} 280 nm) at rt while oxygen-free nitrogen was bubbled through the solution.. The THF was evaporated and the crude solid was recrystallized from $CHCl_3$/ether furnishing the photoadduct 132 (450 mg) in 47 % yield as colorless plates.



$C_{24}H_{26}O_{10}$

474.45

Mp 198°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300- 3500 (br), 1720 (s), 1590 (s).

^1H nmr δ (ppm) 2.87 (s, OH), 3.19 (dd, J=12.0, 3.0 Hz, 1H), 3.42 (dd, J=12.0, 10.5 Hz, 1H), 3.50 (s, 3H), 3.75 (s, 3H), 3.79 (s, 6H), 3.85 (s, 3H), 4.02 (d, J=10.0 Hz, 1H), 5.07 (d, J= 3.0 Hz, 1H), 5.89 (s, 2H), 6.47 (s, 1H), 6.54 (s, 2H), 6.77 (s, 1H).

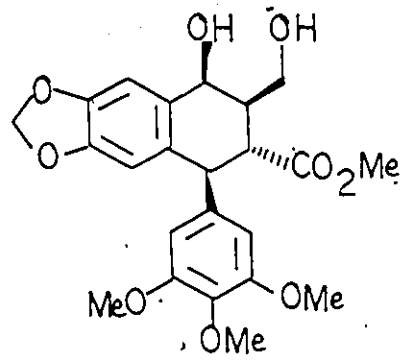
^{13}C nmr δ (ppm) 50.09, 51.79, 52.33, 56.19, 60.88, 68.00, 101.22, 106.04, 108.64, 108.93, 131.74, 138.29, 146.62, 148.19, 152.96, 153.28, 172.75, 174.92.

M.S. m/e 474 (M^+), 456 ($M-H_2O$), 425 ($456-H_3CO^\cdot$), 396 ($425-HCO^\cdot$), 337 (396 - CO).

Analysis Calcd. for $C_{24}H_{26}O_{10}$: C, 60.75; H, 5.53.
Found: C, 61.13; H, 5.71.

Reduction of the diester 132 with $LiEt_3BH$

The diester 132 (474 mg, 1.0 mmol) was dissolved in 10 ml of dry THF and cooled to -78°C under a N_2 atmosphere. $LiEt_3BH$ (3.0 ml, 3 mmol) was added slowly by syringe and the solution was stirred at -78° for 2h. and then at rt for an additional 18 h. Addition of 1% HCl (10 ml) followed by extraction once with ether and three times with CH_2Cl_2 afforded a yellowish colored solid. Recrystallization from ether/hexanes furnished the diol ester 133 (312 mg, 70%) as small colorless needles.



$C_{23}H_{26}O_9$

446.44.

Mp 155°C

IR ($CHCl_3$) υ_{max} (cm^{-1}). 3350-3550 (br), 1725 (s), 1600 (s).

^1H nmr δ (ppm) 2.45 (m, 1H), 3.00 (t, J=11.0 Hz, 1H), 3.52 (s, 3H), 3.79 (s, 6H), 3.84 (s, 3H), 3.80 (br, 2×OH), 4.02-4.28 (m, 3H), 5.01 (d, J=3.0 Hz, 1H), 5.89 (s, 2H), 6.26 (s, 1H), 6.30 (s, 2H), 6.83 (s, 1H).

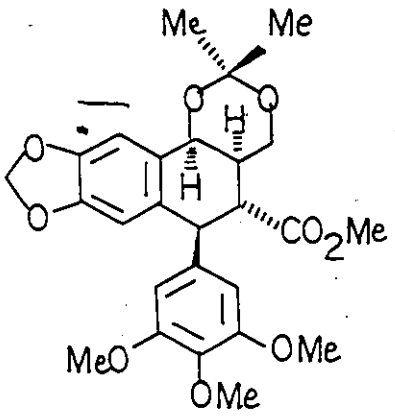
M.S. m/e 446 (M^+), 428 ($M-H_2O$).

Analysis Calcd. for $C_{23}H_{26}O_9$: C, 61.87; H, 5.87.

Found: C, 61.63, H, 5.55.

Preparation of the isopropylidene derivative 134

The diol 133 (340 mg, 0.76 mmol), pTsOH (10 mg) and 2,2-dimethoxypropane (5ml) were stirred at rt for 3 h. The solution was diluted with CH_2Cl_2 and washed with 10 % $NaHCO_3$, dried and the solvent evaporated. Recrystallization from ether/hexanes afforded 330 mg (90%) of 134 as colorless needles.



$C_{26}H_{30}O_9$

486.50

Mp 181-182°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 1720 (s), 1590 (s).

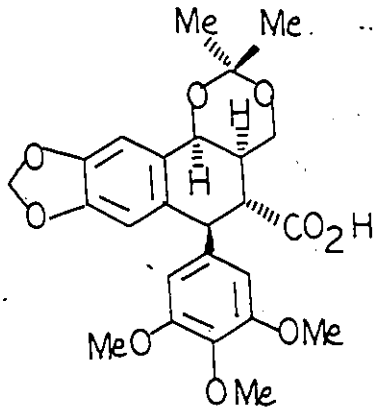
^1H nmr δ (ppm) 1.47 (s, 3H), 1.63 (s, 3H), 2.03 (m, 1H), 3.40 (t, J=11.6 Hz, 1H), 3.43 (s, 3H), 3.65 (dd, J=12.0, 2.0 Hz, 1H), 3.75 (s, 6H), 3.80 (s, 3H), 4.06 (d, J= 11.6 Hz, 1H), 4.18 (dd, J=12.0, 3.5 Hz, 1H), 4.83 (d, J=3.0 Hz, 1H), 5.87 (d, J=1.4 Hz, 1H), 5.91 (d, J=1.4 Hz, 1H), 6.23 (s, 1H), 6.30 (s, 2H), 6.67 (s, 1H),

M.S. m/e 486 (M^+).

Analysis Calcd. for $C_{26}H_{30}O_9$: C, 64.18; H, 6.22.
Found: C, 64.12; H, 5.96.

Saponification of the ester 134

The ester 134 (50 mg) was saponified in a 1:1 mixture of 1% KOH and dioxane (total volume of 10 ml) by heating the solution to reflux for 4 h. Ether was added to the cooled solution and the aqueous phase was separated and acidified. The acid was extracted from the aqueous phase with three times 10 ml of CH_2Cl_2. The combined organic extracts were dried and the solvent evaporated affording the acid derivative 135 (40 mg, 83%) as a colorless powder.



$C_{25}H_{28}O_9$

472.47

Mp 181-183°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 2500-3500 (br), 1700 (s), 1590 (s).

^1H nmr δ (ppm) 1.46 (s, 3H), 1.63 (s, 3H), 2.01 (m, 1H), 3.48 (t, J=11.6 Hz, 1H), 3.69 (dd, J=12.0, 2.0 Hz, 1H), 3.80 (s, 6H), 3.85 (s, 3H), 4.01 (d, J=11.6 Hz, 1H), 4.09 (dd, J=12.0, 3.5 Hz, 1H), 4.81 (d,

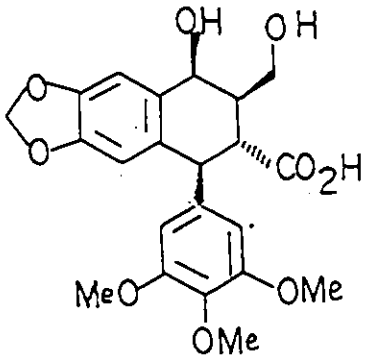
J=3.0 Hz, 1H), 5.86 (d, J=1.4 Hz, 1H), 5.88 (s, J=1.4 Hz, 1H), 6.24 (s, 1H), 6.35 (s, 2H), 6.71 (s, 1H).

M.S. m/e 472 (M^+).

Analysis Calcd. for $C_{25}H_{28}O_9$: C, 63.55; H, 5.97.
Found: C, 63.20; H, 6.17.

Conversion of 135 to epiisopodophyllic acid 136

The isopropylidene protecting group of 135 was hydrolysed in a 1:1 mixture of 1% HCl (aqueous) and dioxane by stirring at rt for 24 h. Normal workup afforded after recrystallization from acetone/ether epiisopodophyllic acid, 136 (100 mg, 85%) as small colorless needles.



$C_{22}H_{24}O_9$

432.41

Mp 230-234°C (dec.)

IR ($CHCl_3$) υ_{max} (cm^{-1}) 2500-3500 (br), 1710 (s), 1590 (s).

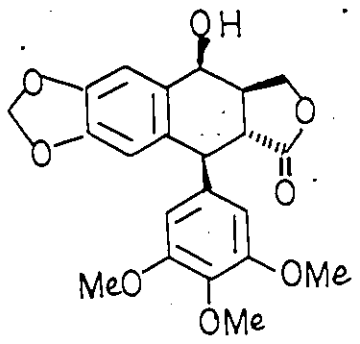
^1H nmr δ (ppm) 2.47 (m, 1H), 3.08 (t, J=11.0 Hz, 1H), 3.79 (s, 6H), 3.84 (s, 3H), 3.95 (br, 3×OH), 4.00-4.27 (m, 3H), 5.07 (d, J= 3.0 Hz, 1H), 5.85 (s, 2H), 6.26 (s, 1H), 6.30 (s, 2H), 6.82 (s, 1H).

M.S. m/e 432 (M^+).

Analysis Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.60.
Found: C, 61.28; H, 5.69.

Conversion of epiisopodophyllic acid to epiisopodophyllotoxin 114

Epiisopodophyllic acid , 136 (50 mg, 0.12 mmol) and DCC (30 mg, 0.12 mmol) were dissolved in 4 ml of THF and the resulting solution was stirred for 3 h at rt. Water (0.2 ml) and glacial acetic acid (0.1 ml) were added and the solution was stirred for an additional 30 minutes. The solvent was evaporated and the residue was taken up in 5 ml of CH_2Cl_2 and the dicyclohexylurea was filtered for removal. The filtrate was dried and the solvent evaporated. Purification by PTLC (ether) afforded the lactone, 114 (37 mg, 75%) as a colorless powder.



$C_{22}H_{22}O_8$

414.40

Mp 258-260°C (dec.) , (lit. mp.272°, dec.)[75]

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3350-3550 (br), 1775 (s), 1590 (s).

^1H nmr δ (ppm) 2.03 (br, OH), 2.68 (m, 1H), 3.29 (dd, J=14.0, 11.2 Hz, 1H), 3.82 (s, 6H), 3.85 (s, 3H), 4.03 (d, J= 10.0 Hz, 1H), 4.11 (m, 1H), 4.46 (m, 1H), 4.94 (d, J= 3.0 Hz, 1H), 5.93 (s, 2H), 6.39 (s, 1H), 6.44 (s, 2H), 6.78 (s, 1H).

M.S. m/e 414 (M^+).

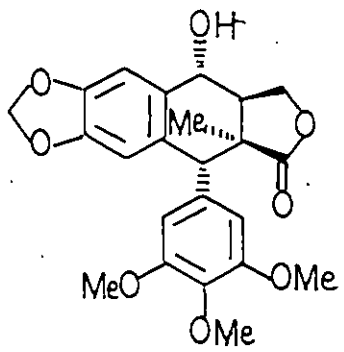
Analysis Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35.

Found: C, 63.89; H, 5.41.

PART 2

Preparation of the dianion of podophyllotoxin and subsequent reaction with methyl iodide

Podophyllotoxin ,6 (207 mg, 0.5 mmol) was dissolved in a small volume of dry THF and added slowly to a cooled (-78°C) solution of LDA (2 equivalents), prepared from diisopropylamine (0.29 ml) and n-BuLi (0.83 ml, 2.4 M in hexanes) in 5 ml of dry THF. The yellow solution was stirred for 15 minutes at -78° and then excess CH_3I (0.25 ml) was added. The solution was warmed to rt and stirred for an additional 18 h. The usual workup followed by column chromatography on silica gel (hexanes/ethyl acetate; 1:1) afforded two components which were obtained as beige powders after precipitation from ether/ hexanes. The major component (112 mg, 53%) was identified as 2-methylpicropodophyllotoxin , 142, and the minor component was identified as 2-methylpodophyllotoxin (40 mg, 18%), 143.



142

$C_{23}H_{24}O_8$

428.42

Mp 92- 95°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300-3550 (br), 1770 (s), 1590 (s).

^1H nmr δ (ppm) 1.12 (s, 3H), 2.79 (ddd, J= 7.8, 6.0, 1.4 Hz, 1H), 3.79 (s, 6H), 3.80 (s, 3H), 4.23 (s, 1H),

4.57 (d, J=7.8 Hz, 1H), 4.42 (m, 2H), 6.94 (d, J=0.5 Hz, 1H), 6.96 (d, J=0.5 Hz, 1H), 6.65 (s, 1H), 6.76 (s, 1H), 6.78 (s, 2H).

M.S. m/e 428 (M^+).

$[\alpha]_D$ = -107° ($CHCl_3$) c=0.41

Analysis Calcd. for $C_{23}H_{24}O_8$; C, 64.48; H, 5.65.

Found: C, 64.03, H, 6.22.

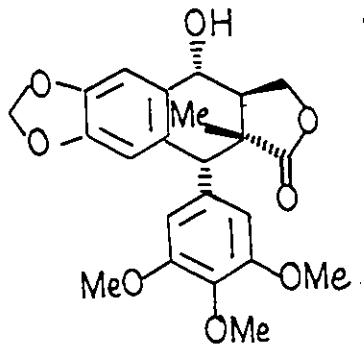
Preparation of 4-O-tetrahydropyranylpodophyllotoxin 144

The THP derivative of podophyllotoxin was prepared in 85% yield according to Gensler [28] using freshly distilled dihydropyran with p-TsOH as the acid catalyst and CH_2Cl_2 as the solvent.

Preparation of the enolate anion of 144 and subsequent reaction with methyl iodide

The THP derivative 144 (400 mg, 0.8 mmol) was dissolved in a small volume of dry THF and added slowly to a cooled solution (-78°) of LDA (one equivalent) , prepared from diisopropylamine (0.23 ml) and n-BuLi (0.48 ml) in 10 ml of dry THF. The yellow solution was stirred for 15 minutes at -78° and then CH_3I was added (0.5 ml) . The solution was warmed to rt and stirred for an additional 18 h. Normal workup afforded a viscous oil which was passed through a short silica gel column to remove any salts prior to hydrolysis of the THP group.

The crude methylation product was hydrolysed by refluxing in 10 ml of a solution of 5% aqueous HCl and THF (1:9) for 4 h. Workup afforded a yellow foam that was separated into three components by HPLC (hexanes/ethyl acetate, 1:1). Each component was precipitated from ether/ hexanes affording beige powders identified as the following in order of elution from the column: picropodophyllotoxin (20 mg, 6%), 2-methylpicropodophyllotoxin 142 (60 mg, 18%) and 2-methylpodophyllotoxin 143 (145 mg, 43 %). 2-Methylpicropodophyllotoxin, 142 was identical in all respects to that product obtained via the dianion route.



143

$C_{23}H_{24}O_8$

428.42

Mp 101-103°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3350-3550 (br), 1780 (s), 1590 (s).

^1H nmr δ (ppm) 400 MHz , 1.32 (s, 3H), 2.89 (ddd, J=7.5, 10.5, 11.0 Hz, 1H), 3.75 (s, 6H), 3.81 (s, 3H), 4.17 (dd, J=9.0, 10.5 Hz, 1H), 4.26 (s, 1H), 4.51 (dd, J= 7.5, 9.0 Hz, 1H), 4.70 (d, J=11.0 Hz, 1H), 5.98 (d, J=0.5 Hz, 1H), 5.97 (d, J=0.5 Hz, 1H), 6.36 (s, 1H), 6.36 (s, 2H), 6.48 (s, 1H), 7.10 (s, 1H).

^{13}C nmr δ(ppm) 22.50, 46.72, 48.74, 50.74, 56.24, 60.85, 72.02, 73.18, 101.29, 107.23, 107.93, 109.64, 129.27, 131.81,

135.87, 136.84, 147.37, 148.13, 152.42, 153.13, 180.83.

M.S. m/e 428 (M^+)

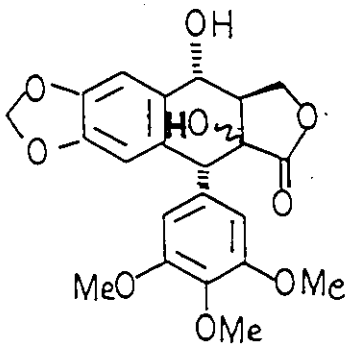
$[\alpha]_D$ ($CHCl_3$) = -118°, c=0.43

Analysis Calcd. for $C_{23}H_{24}O_8$: C, 64.48, H, 5.65;

Found : C, 64.39, H, 5.61.

Trapping of the enolate anion prepared from 144 with oxygen

Treatment of 144 (498 mg, 1.0 mmol) with 1 equivalent of LDA in dry THF at -78°C produced a clear yellow solution of the enolate anion that was trapped with oxygen by bubbling dry oxygen through the solution for 30 minutes. The solution was warmed to rt and stirred for an additional hour. The reaction mixture was treated with a saturated solution of sodium sulfite to reduce the intermediary hydroperoxides. Normal workup followed by hydrolysis of the crude product afforded a yellow foam which was purified by column chromatography on silica gel (hexanes/ethyl acetate; 1:1). Precipitation from ether/hexanes furnished 350 mg (80%) of a colorless powder which was shown by nmr to be a 1:1 mixture of 2-hydroxypodophyllotoxin 146 and 2-hydroxypicropodophyllotoxin 147. These isomers were not separable.



146 + 147

$C_{22}H_{22}O_9$

430.40

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300-3550 (br), 1775 (s), 1590 (s).

^1H nmr δ (ppm) 2.60-3.33 (m, 2H), 3.79+3.74 (s, 6H), 3.87+3.83 (s, 3H), 4.25 (m, 3H), 4.90 (m, 1H), 5.96 (br, 2H), 6.38+6.46 (s, 2H), 6.49+6.34 (s, 1H), 7.04+7.10 (s, 1H).

M.S. m/e 430 (M^+).

Analysis Calcd. for $C_{22}H_{22}O_9$: C, 61.53; H, 4.93.
Found : C, 61.59; H, 5.08.

Trapping of the enolate anion prepared from 144 with hexachloroethane

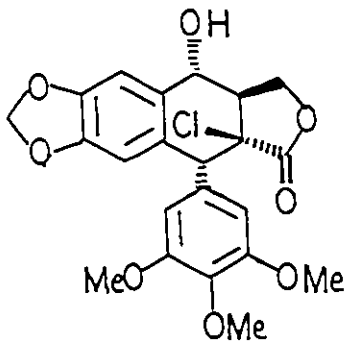
Treatment of 144 (249 mg, 0.5 mmol) with 1 equivalent of LDA in dry THF at -78° followed by trapping with excess hexachloroethane (178 mg) and warming of the solution to rt, stirring for an additional 18 h and normal workup afforded a viscous oil . The crude product was hydrolyzed in a mixture of 5% HCl and THF (1:9). The crude deprotected product was purified by column chromatography (hexanes/ethyl acetate, 1:1) affording only one product (164 mg, 74%) identified as 2-chloropodophyllotoxin , 148.

148

$C_{22}H_{21}O_8Cl$

448.85

Mp 106-110°C



IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300-3550 (br), 1785 (s), 1590 (s)

^1H nmr δ (ppm) 2.79 (d, 7.0 Hz, 1H), 3.07 (ddd, J=7.0, 9.0, 9.5 , 1H), 3.77 (s, 6H), 3.84 (s, 3H), 4.26-4.65 (m, 2H), 4.79 (s, 1H), 4.98 (dd, J=7.0, 9.5 Hz, 1H), 5.97 (d, J=0.5 Hz, 1H), 5.99 (s, J= 0.5 Hz, 1H), 6.44 (s, 2H), 6.49 (s, 1H), 7.09 (s, 1H).

M.S. m/e 448 (M^+), 450 (M+2).

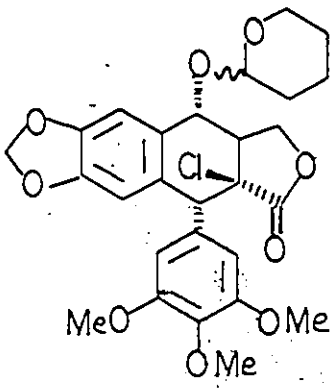
$[\alpha]_D$ ($CHCl_3$) = -133.46 c=0.74.

Analysis Calcd. for $C_{22}H_{21}O_8Cl$: C, 58.86; H, 4.72.

Found : C, 59.03; H, 4.98.

Isolation of 2-chloro-4-O-tetrahydropyranylpodophyllotoxin 149

Upon repeating the chlorination reaction the tetrahydropyranyl derivative, 149 was isolated by column chromatography (hexanes/ ethyl acetate; 2:1) in 80 % yield.



$C_{27}H_{29}O_9Cl$

532.96

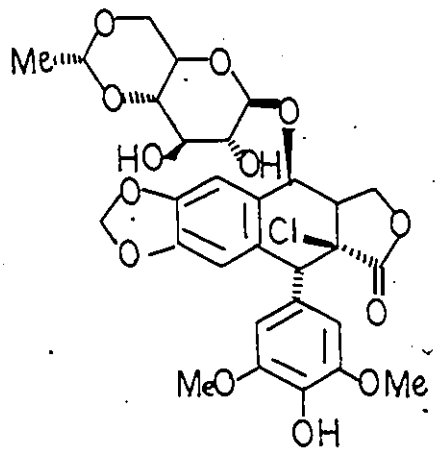
IR ($CHCl_3$) υ_{max} (cm^{-1}) 1785 (s), 1590 (s).

^1H nmr see Figure 6

M.S. m/e 532 (M^+), 534 (M+2).

Preparation of 4'-O-demethyl-2-chloro-1-O-(4,6-ethylidene-β-D-glucopyranosyl)-epipodophyllotoxin 150

4'-O-Demethyl-1-O-(4,6-ethylidene-β-D-glucopyranosyl)-epipodophyllotoxin (VP16, 1.17g, 2.0 mmol) was treated with 4 equivalents of LDA at -78°C followed by hexachloroethane (2.37 g). The solution was warmed to rt and stirred for an additional 18 h. The tetra-anion was not very soluble under these reaction conditions. Workup consisted of washing with saturated sodium sulfite solution and extraction of the aqueous phase three times with CH_2Cl_2, drying and evaporation of the solvent. The crude product was purified by PTLC (hexanes/ethyl acetate; 1:3, 3 runs) affording starting material (800 mg, 70%) and a slightly more mobile compound (125 mg, 10%) identified as 4'-O-demethyl-2-chloro-1-O-(4,6-ethylidene-β-D-glucopyranosyl)-epipodophyllotoxin, 150.



$C_{29}H_{31}O_{13}Cl$
623.00

Mp 155-160°C

IR ($CHCl_3$) υ_{max} (cm^{-1}) 3300- 3550 (br), 1780 (s), 1620 (s)

^1H nmr δ (ppm) 1.37 (d, J=5.0 Hz, 1H), 2.60 (s, 2×OH), 3.20 (m, 1H), 3.28-3.77 (m, 6H), 3.54 (s, 6H),

4.12 (dd, J=8.0, 5.0 Hz, 1H), 4.57 (dd, J=8.0,7.0 Hz, 1H), 4.65 (dd, J=8.7, 8.0 Hz, 1H), 4.72 (s, 1H) 4.73 (q, J=5.0 Hz, 1H), 5.17 (d, J=3.0 Hz, 1H), 5.52 (s, phenolic OH), 5.98 (d, J=0.5 Hz, 1H), 6.00 (d, J=0.5 Hz, 1H), 6.58 (s, 2H), 6.75 (s, 1H), 7.04 (s, 1H).

M.S. m/e 623 (M^+), 625 (M+2).

$[\alpha]_D$ ($CHCl_3$) = -59.35, c=1.30

Analysis Calcd. for $C_{29}H_{31}O_{13}Cl$: C, 55.91; H, 5.02.

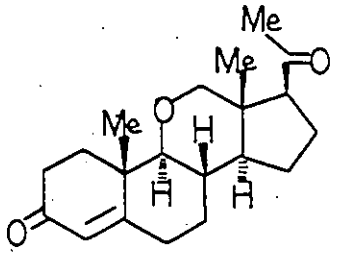
Found : C, 56.02; H, 5.05.

ADDENDUM

Attempted Synthesis of 11-Oxaestrone

The first synthesis of a heterocyclic analogue of a naturally occuring steroidal estrogen was 4-azaestradiol-17-acetate, first prepared by Uskolović and Gut in 1959.[95] Since that time, a tremendous number of syntheses of hetero-estrogen analogues have been reported because of the interest in these compounds as potential drugs.[96] The first oxaestrone analogue whose synthesis was reported was 6-oxaestrone, in 1964.[97]

In the progesterone steroids substitution of the 11-position by a hetero-atom, such as the preparation of 11-oxaprogesterone, 151, by Engel et al, in 1972,[98] produced compounds having increased activity. 11-Oxaprogesterone, 151 was shown to possess a 2 to 2.5 fold increase in ovulation inhibiting activity when compared with progesterone itself.

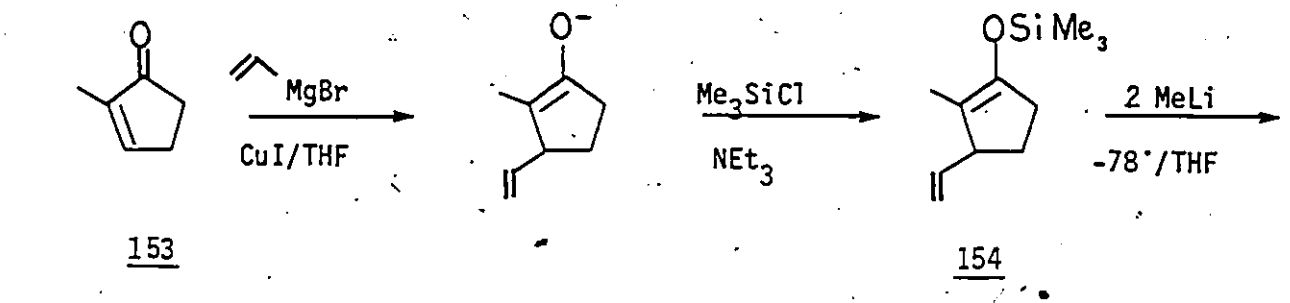


151

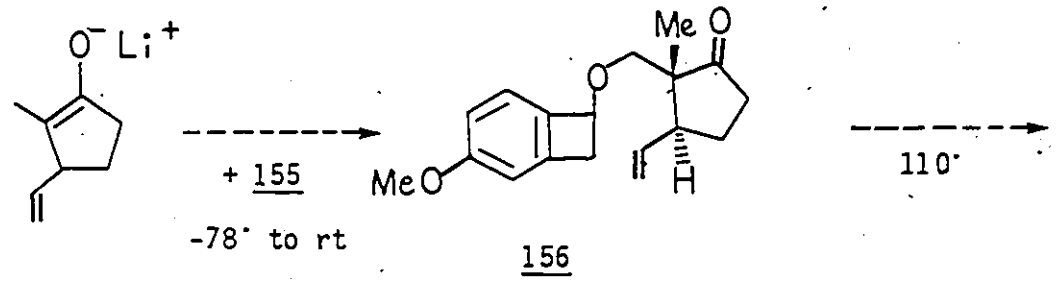
We initiated a program to synthesize 11-oxaestrone based on our interest in the intramolecular cycloaddition reactions of o-quinodimethanes. As was mentioned earlier in this thesis, A-ring aromatic steroids have been one of the most popular targets for the intramolecular cycloaddition reaction of o-quinodimethanes. The two major contributors to this area have been Kametani and Oppolzer, both of whom have published syntheses of optically active estradiol (See results and Discussion, Part 1).

It was our hope that 4-methoxybenzocyclobutenol, 93 would serve as a convenient entry into the synthesis of 11-oxaestrone 152. Our synthetic approach was modeled after the work of Oppolzer.[99] The source of the D-ring was to be 2-methylcyclopent-2-ene-1-one 153.[100] It is well known that α,β-unsaturated ketones such as 153 undergo conjugate addition with alkyl cuprates such as vinyl cuprate and that the resulting enolate can be trapped with chlorotrimethylsilane to form the corresponding silyl enol ether , in this case, 154.[101] The enolate can then be regenerated by treatment of the silyl enol ether with two equivalents of methyllithium at -78°C in THF.[102]

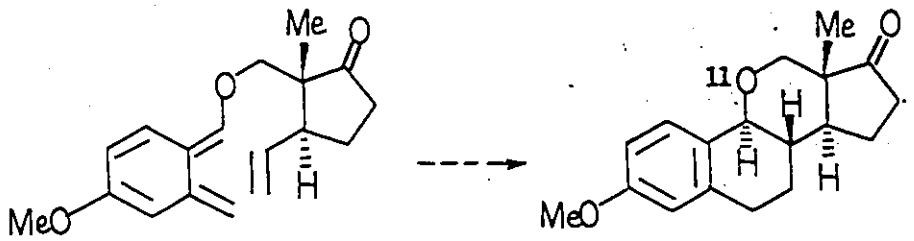
The enolate could then be trapped with the very electrophilic O-chloromethyl-4-methoxybenzocyclobutenol, 155, which might be prepared from 4-methoxybenzocyclobutenol 93 by treatment with paraformaldehyde and gaseous HCl at low temperature, affording the desired ether , 156. With both pieces joined all that would remain to be done would be to heat compound 156 to approximately 110°C causing thermal ring opening of the cyclobutenol in the manner



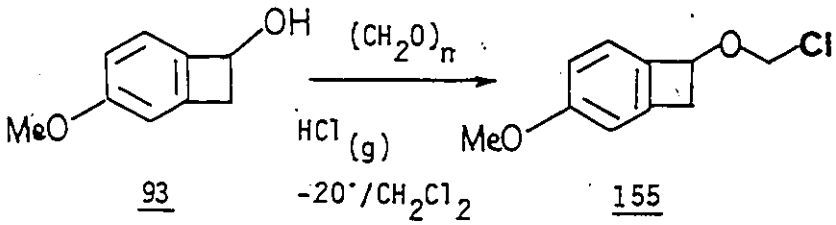
153 154



156



157 152 11-OXAESTRONE METHYL ETHER



93 155

SCHEME 28

discussed earlier. This would produce the o-quinodimethane intermediate, 157 which should undergo intramolecular trapping by the vinyl group to give the desired 11-oxaestrone methyl ether in only three steps from 4-methoxybenzocyclobutenol.

What appeared to be a straightforward, brief synthesis turned out to be plagued with a number of serious difficulties which were never completely resolved. I wish to report what has been completed in this synthesis and what exactly the major stumbling block is.

2-Methylcyclopent-2-ene-1-one 93 was converted to 1-O-trimethylsilyl-3-vinyl-2-methylcyclopent-1-ene-1-ol 154 by the (1,4) addition of vinyl magnesium bromide in the presence of CuI[103] and trapping of the intermediate enolate with chlorotrimethylsilane.

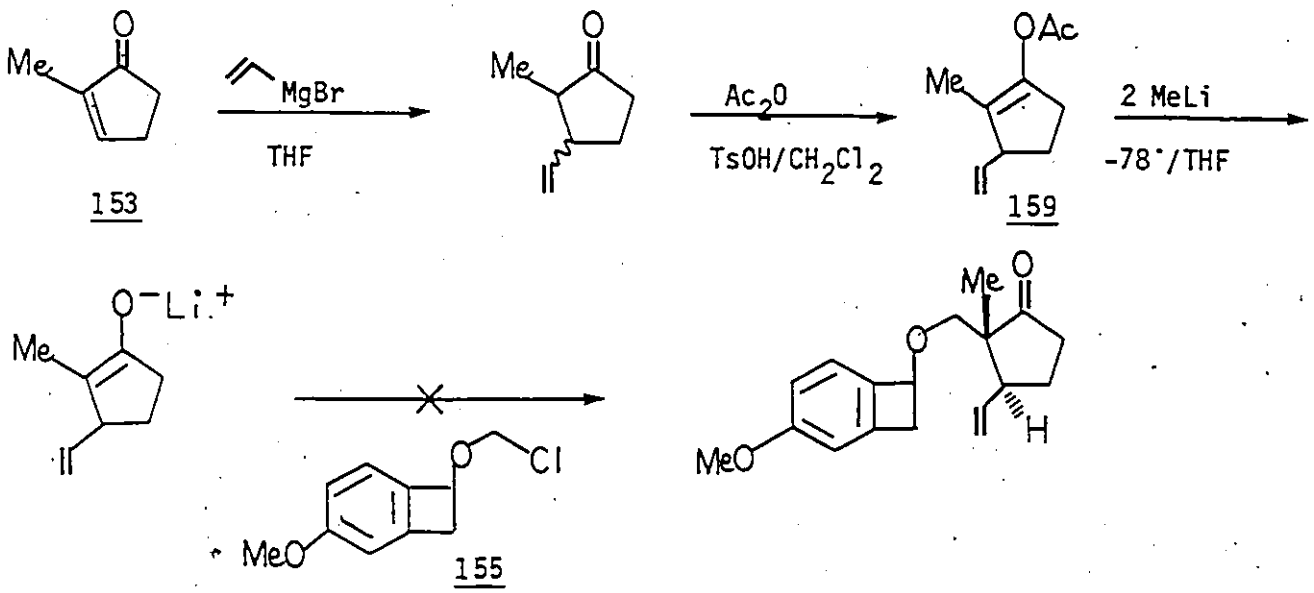
O-chloromethyl-4-methoxybenzocyclobutenol 155 was prepared by treatment of 4-methoxybenzocyclobutenol with paraformaldehyde and gaseous HCl at -20°C in methylene chloride. The crude product, a colorless oil , was used without purification due to its instability. The ^{1}H nmr spectra of 155 indicated the presence of the $-OCH_2Cl$ moiety by a singlet at δ= 4.89 ppm integrating for 2H.

Treatment of the silyl enol ether, 154 with two equivalents of methyllithium and then the chloromethyl ether 155 at -78°C in dry THF failed to produce any of the desired coupled product. The only isolated products were 2-methyl-3-vinylcyclopent-2-ene-1-one and 1-chlorobenzocyclobutene . The latter product may arise from the decomposition of the chloromethyl ether.

The enol acetate, 159 was also prepared , by treatment of 2-methyl-3-vinylcyclopentan-1-one with acetic anhydride and TsOH

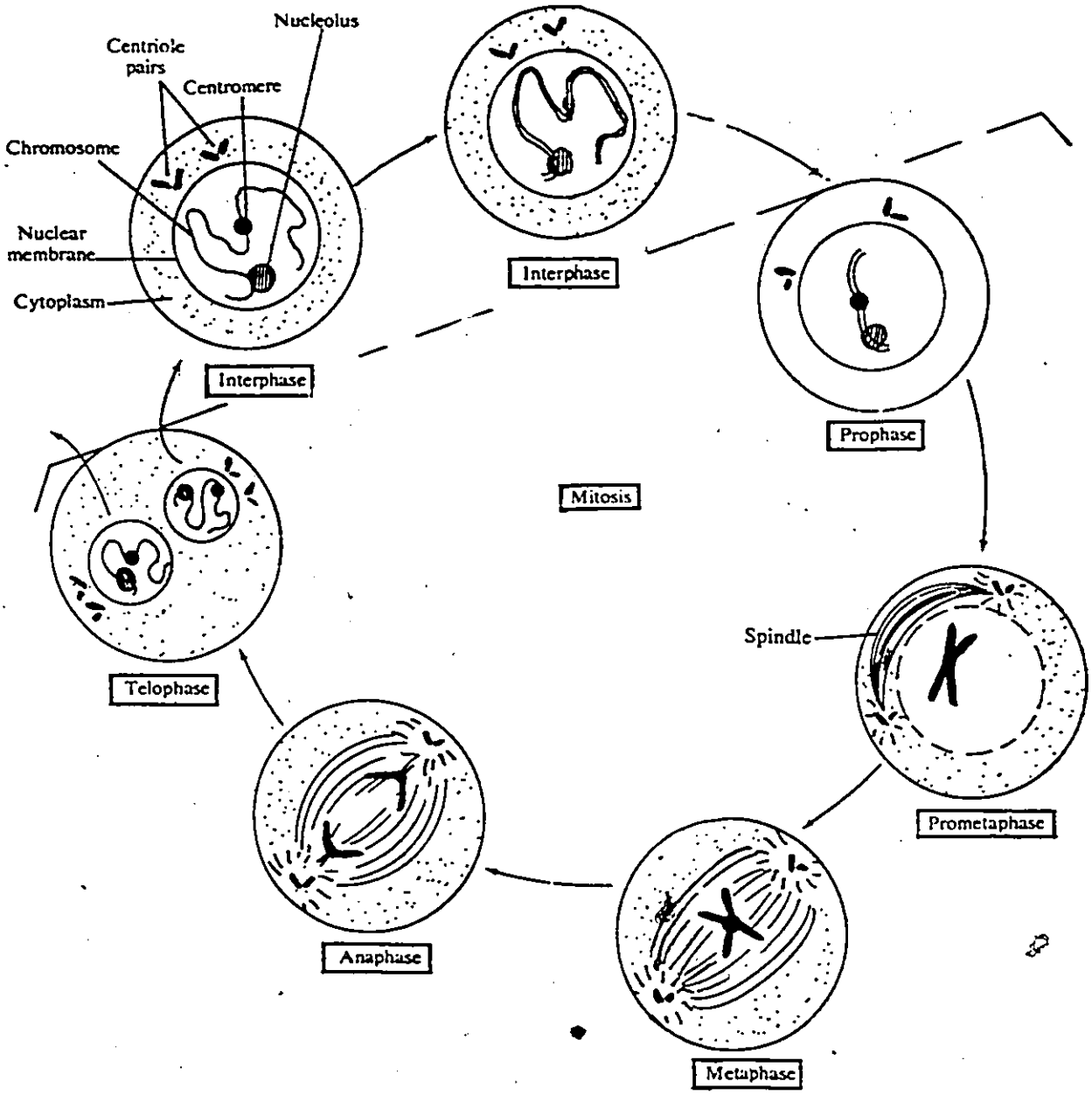
in methylene chloride. Treatment of 159 with 2 equivalents of methyllithium produced the enolate but all attempts to trap this enolate with the chloromethyl ether, 155 were unsuccessful.

Thus, the stumbling block in this synthesis was the coupling of the two fragments (154 + 155) and the failure to accomplish this step appeared to reside in the instability of the chloromethyl ether fragment, 155. Any attempts at purification of this material or prolonged storage at even low temperature (freezer) resulted in conversion to the chloride, 158, presumably via a carbonium ionic process. This project was abandoned by this worker due to the lack of time although I do believe that under the appropriate conditions the coupling reaction could be successful, perhaps, through the enthusiastic pursuits of another student.



APPENDIX

The Stages of Cell Division



CLAIMS TO ORIGINAL RESEARCH

1. Two new routes to the synthesis of podophyllotoxin analogues were developed. One involved the intramolecular cycloaddition reaction of thermally generated o-quinodimethane intermediates derived from the appropriately substituted benzocyclobutenols. The second route involved photoenolisation of o-alkyl-substituted benzaldehydes and subsequent trapping of the dienol intermediate.

2. Total syntheses of (±)-epiisopodophyllotoxin and (±)-epiisopodophyllic acid were reported. The synthesis of the latter constitutes a formal synthesis of podophyllotoxin.

3. Two new short syntheses of 6-(3',4',5'-trimethoxybenzyl)piperonal were reported.

4. A method was devised for the synthesis of C_2 substituted podophyllotoxin derivatives where the trans lactone product was the major one , starting with the tetrahydropyranyl derivative of podophyllotoxin. In this manner methyl, chloro and hydroxyl substituents were introduced. The biological test results against L1210 and P388 leukemias were reported.

5. The C_2 chloro derivative of VP-16 was prepared and found to have antitumour activity in the L1210 test comparable to VP-16, the currently used clinical agent.

6. The following is a list of the new compounds that were prepared and completely characterized including elemental analysis:

1. 2-bromo-5-methoxystyrene oxide
2. 4-methoxybenzocyclobutenol 93
3. compound 90
4. 2-bromo-4,5-(methylenedioxy)styrene oxide 100
5. 4,5-(methylenedioxy)benzocyclobutenol 97
6. compound 104
7. compound 116
8. compound 117
9. compound 118
10. compound 119
11. compound 120
12. compound 121
13. compound 122
14. compound 123
15. compound 125
16. 1-bromo-4,5-(methylenedioxy)-2-(3',4',5'-trimethoxybenzoyl)benzene 130
17. 1-bromo-4,5-(methylenedioxy)-2-(3',4',5'-trimethoxybenzyl)benzene 131
18. compound 132
19. compound 133
20. compound 134
21. compound 135
22. 2-methylpicropodophyllotoxin 142

23. 2-methylpodophyllotoxin 143
24. 2-hydroxypicropodophyllotoxin 147
25. 2-hydroxypodophyllotoxin 146
26. 2-chloropodophyllotoxin 148
27. 4'-O-demethyl-2-chloro-1-O-(4,6-ethylidene-β-D-glucopyranosyl)-epipodophyllotoxin 150

REFERENCES

1. Haworth, R.D., Natural Resins, Ann. Rep. Chem. Soc. (London), 33, 266 (1936).
2. Cooley, G., Farrant, R.D., Kirk, D.N., Wynn, S., Tetrahedron Lett., 22, 349 (1981).
3. Muenscher, W.C., Poisonous Plants of the United States, New York, MacMillan Co., page 94, 1939.
4. Hartwell, J.L., Schrecker, A.W., The Chemistry of Podophyllum, Fortsch. Chem. Org. Natur., XV, 6-166 (1958).
5. King, J.,Coll. J. Med. Sc., 2, 557 (1857).
6. Lloyd, J.U., The Ecletric Alkaloids, Bull. Lloyd Library of Botany,Pharmacy and Materia Medica, Pharmacy Ser. #2, Bull. #12, 7-10 (1910).
7. Kaplan, I.W., Condylomata Acuminata, New Orleans Med. Surg. J., 94, 388 (1942).
8. Kelly, M.G., and Hartwell, J.L., J. Nat. Cancer Inst., 14, 967 (1954).
9. Podwyssotzki, V.,Pharmacologische Studien über Podophyllum Peltatum, Arch. Exp. Pathol. Pharmakol.,13. 29 (1880).
10. Petcher, J.J., Weber, H.P., Kuhn, M.,and von Wartburg, A., J. Chem. Soc. Perkin II, 288 (1973).
11. Gensler, W.J., and Gatsonis, C.D., J. Org. Chem., 31, 3224 (1966).
12. Gensler, W.J., and Gatsonis , C.D.,J. Org. Chem., 31 , 4004 (1966).
13. Cornman, I., and Cornman, M.E., Ann. N.Y. Acad. Sci., 51, 1443 (1951).

14. Metzler, D.E., Biochemistry, Academic Press, New York,1977, p.206.

15. Dustin, P.Jr., Pharmacol. Rev., 15, 449 (1963).

16. Cortese, F., Bhattacharyya, B., Wolff, J., J. Biol. Chem., 252, 1134 (1977).

17. Loike, J.D., and Horwitz, S.B., Biochemistry, 15, 5443 (1976).

18. Kuhn, M., and von Wartburg, A., Helv. Chim. Acta , 51, 163 (1968).

19. Kuhn, M., and von Wartburg, A., Helv. Chim. Acta , 51 1631 (1968).

20. Keller-Juslén, C., Kuhn, M.,von Wartburg, A., Stähelin, H., J. Med. Chem., 14, 936 (1971).

21. a) Issell, B.F., Crooke, S.T., Cancer Treatment Rev., 6, 107 (1979).

b) Radice, P.A., Bunn, P.A.Jr., Ihde, D.C., Cancer Treatment Rep., 63, 1231 (1979).

c) Eagen, R.T., Carr, D.T., Frytak, S., Rubin, J., Lee, R.E., Cancer Treatment Rep., 60, 949 (1976).

d) Drewinko, B., and Barlogic, B., Cancer Treatment Rep., 60 1295 (1976).

22. Stähelin, H., and Poschmann, G., Oncology, 35, 217 (1978).

23. Loike, J.D., and Horwitz, S.B., Biochemistry, 15 5435 (1976).

24. Jardine, I., Anticancer Agents Based on Natural Product Models, Academic Press, pages 319-351 (1980).

25. Private communication.

26. a) Gensler, W.J., and Wang, S.Y., J. Am. Chem. Soc., 76, 5896 (1954).

b) Gensler, W.J., Samour, C.M., and Wang, S.Y., J. Am. Chem. Soc., 76, 315 (1954).

27. Gensler, W.J., and Gatsonis, C.D., J. Org. Chem., 31, 3224 (1966).

28. Gensler, W.J., and Gatsonis, C.D., J. Org. Chem., 31, 4004 (1966).

29. Kende, A.S., Liebeskind, L.S., Mills, J.E., Rutledge, P.S., Curran, D.P., J. Am. Chem. Soc., 99, 7082 (1977).

30. Kende, A.S., King, M.L., Curran, D.P., J. Org. Chem., 40, 2828 (1981).

31. Rodrigo, R., J. Org. Chem., 45, 4538 (1980).

32. Plaumann, H.P., Smith, J.G., Rodrigo, R., J. Chem. Soc. Chem. Comm., 354 (1980).

33. Rajapaska, D., Rodrigo, R., J. Am. Chem. Soc., 103, 6208 (1981).

34. Renz, J., Kuhn, M., von Wartburg, A., Liebigs. Ann. Chem., 681, 207 (1965).

35. Dwahan, K.L., Gowland, B.D., and Durst, T., J. Org. Chem., 45, 922 (1980).

36. Akgün, E, Glinski, M.B., Dhawan, K.L., Durst, T., J. Org. Chem. 46, 2730 (1981).

37. Oppolzer, W., Synthesis, 793 (1978).

38. Diels, O., and Alder, K., Justus Liebigs Ann. Chem., 460,98 (1928).

39. Alder, K., and Schumacher, M., Fortschr. Chem. Org. Naturst., 10, 66 (1953).

40. Cava, M.P., and Napier, D.R., J. Am. Chem. Soc., 79, 1701 (1957).

41. McOmie, J.F.W., Perry, D.H., Synthesis, 416 (1973) and earlier work cited herein.

42. Cava, M.P., Deana, A.A., J. Am. Chem. Soc., 81, 4266 (1959).

43. Jung, F., Molin, M., Van den Elzen, R., Durst, T., J. Am.Chem.Soc., 96, 935 (1974).

44. Spangler, R.J., Beckmann, B.G., Kim, J.H., J. Org. Chem., 42, 2989 (1977).

45. Flynn, C.R., and Michl, J., J. Am. Chem. Soc., 96, 3280 (1974).

46. Sammes, P.G., Tetrahedron, 32, 405 (1976) and earlier work cited herein.

47. Ito, Y., Nakatsuka, M., Saegusa, T., J. Am. Chem. Soc., 102, 863 (1980).

48. Bunnett, J.F., Skorcz, J.A., J. Org. Chem., 27, 3836 (1962).

49. Wasserman, H.H., Solodar, J., J. Am. Chem. Soc., 87, 4002 (1965).

50. Stevens, R.V., and Bisacchi, G.S., J. Org. Chem., 47, 2393 (1982).

51. Woodward, R.B., and Hoffmann, R., Angew. Chemie. Int. Ed., 8, 781 (1969).

52. Huisgen, R., and Seidl, H., Tetrahedron Lett., 3381 (1964).

53. Oppolzer, W., Tetrahedron Lett., 1001 (1974).

54. Oppolzer, W., and Keller, K., J. Am. Chem. Soc., 93, 3836 (1971).

55. For a recent review on this topic see: Funk, R.L., and Vollhardt, K.P.C., Chem. Soc. Reviews, 9, 41 (1980).

56. Kametani, T., Matsumoto, H., Nemoto, H., Fukumoto, K., Tetrahedron Lett., 2425 (1978).

57. Oppolzer, W., and Roberts, D.A., Helv, Chim. Acta, 63, 1703 (1980).

58. Kametani, T., Suzuki, K., Nemoto, H., J. Org. Chem., 47, 2331 (1982).

59. Letsinger, R.L., and Ogilvie, K.K., J. Org. Chem., 32, 286 (1967).

60. Arnold, B.J., Sammes, P.G., Wallace, T.W., J. Chem. Soc. Perkin I, 409 (1974).

61. Pola, J., and Chvalovsky, V., Collection Czechoslov. Chem. Commun., 40, 2494 (1975).

62. Orr, A., Robinson, R., Williams, M., J. Chem. Soc., 946 (1917).

63. a) Rambaud, B.J., Bull. Soc. Chim. Fr., 1, 1317 (1934).

b) Tufariello, J.J., and Tette, J.P., J. Org. Chem., 40, 3866, (1975).

64. see reference 60.

65. Huffman, K.R., Loy, M., and Ullman, E.F., J. Am. Chem. Soc., 87, 5417 (1965).

66. Yang, N.C., and Rivas, C., J. Am. Chem. Soc., 83, 2213 (1961).

67. Sammes, P.G., Tetrahedron, 32, 405 (1976).

68. Block, E., and Stevenson, R., J. Chem. Soc. Perkin I, 308 (1973).

69. Arnold, B.J., Mellows, S.M., and Sammes, P.G., J. Chem. Soc. Perkin I, 1266 (1973).

70. Hoffman, R., and Woodward, R.B., J. Am. Chem. Soc., 87 4388 (1965).

71. Scholz, D., Monatsh. Chem., 110, 1471 (1979).

72. Lane, C.F., Aldrichimica Acta, 7, 32 (1974).

73. Ireland, R.E., and Thompson, W.J., Tetrahedron Lett., 4705 (1979).

74. Kuhn, M., and von Wartburg, A., Helv. Chim. Acta , 46, 2127 (1963).

75. Hartwell, J.L., and Schrecker, A.W., Fortschr. Chem. Naturstoffe, 15, 83 (1958).

76. Plaumann, H.P., Smith, J.G., Rodrigo, R., J. Chem. Soc. Chem. Comm., 354 (1980).

77. Kleinberg, J., Inorganic Synthesis, VII, 10 (1963).

78. a) Damon, R.E., Schlessinger, R.H., Blount, J.F., J. Org. Chem., 41, 3773 (1976).

b) Kende, A.S., and L beskind, L.S., J. Am. Chem. Soc., 98, 267 (1976).

79. Graebe, C., and Suter, M., Annalen, 340, 222 (1905).

80. Corey, E.J., and Suggs, W., Tetrahedron Lett., 2647 (1975).

81. Martin, E.L., J. Am. Chem. Soc., 58, 1438 (1936).

82. Gensler, W.J., Samour, C.M., Wang, S.Y., J. Org. Chem., 76, 315 (1954).

83. Renz, J., Kuhn, M., von Wartburg, A., Liebigs Ann. Chem., 681, 207 (1965).

84. Brewer, C.F., Loike, J.D., Horwitz, S.B., Sternlicht, H., Gensler, W.J., J. Med.Chem., 22, 215 (1979).

85. a) Kocsis, J.J., Walaszek, E.J., Geiling, E.M.K., Arch Intern. Pharmacodyn. Ther., 111, 134 (1957).

b) Kelly, M.G., Leiter, J., Bourke, A.R., Smith, P.K., Cancer Res., 11, 263 (1951).

c) Allen, L.M., Marcks, C., Creaven. P.J., Am. Assoc. Cancer. Res. Proc., Abstr. No. 21 (1976).

86. a) Emmenegger, H., Stähelin, H., Rutschmann, J., Renz, J., and von Wartburg, A., Arzneim. Forsch., 11 327, 459 (1978).

b) Loike, J.D., Brewer, C.F., Sternlicht, H., Gensler, W.J., Horwitz, S.B., Cancer. Res., 38, 2688 (1978).

87. Ayres, D.C., Harris, J.A., Jenkins, P.N., Phillips, L., J. Chem. Soc. Perkin I, 1343 (1972).

88. Gensler, W.J., Judge, J.F.X., Leeding, M.V., J. Org. Chem., 37, 1062 (1972).

89. Gensler, W.J., Murthy, C.D., Trammell, M.H., J. Med. Chem., 20, 635 (1977).

90. see reference 86 b).

91. Gensler, W.J., and Gatsonis, C.D., J. Org. Chem., 31, 4004 (1966).

92. Buncel, E., and Durst, T., Comprehensive Carbanion Chemistry, Part A, Elsevier, Amsterdam, page 202 (1980).

93. The diastereomeric ratio was determined by inspection of the 360 MHz ^1H nmr spectra.

94. Geran, R.I., Greenberg, N.H., MacDonald, M.M., Schumacher, A.M., Abbott, B.J., Cancer Chemotherapy Reports, Part 3, Vol. 3, No. 2, 1-87 (1972).

95. Uskoković, M., and Gut, M., Helv. Chim. Acta , 42, 2258 (1959).

96. Morand, P., and Lyall, J., Chem. Rev., 68 85 (1968).

97. Smith, H., Douglas, G.H., Walk, C.R., Experientia, 20, 418 (1964).

98. Engel, R.L., Steroids, 19, 1 (1972).

99. Oppolzer, W., Petrzieka, M., Bättig, K., Helv. Chim. Acta , 60, 2965 (1977).

100. Gassman, P.G., and Pascone, J.M., J. Am. Chem. Soc., 95, 7801, (1973).

101. Boeckman,Jr., R. K., J. Org. Chem., 38, 4450 (1973).

102. House, H.O., Czuba, L.J., Gall, M., and Olmstead, H.D., J. Org. Chem., 34, 2324 (1969).

103. Kametani, T., Nemoto, H., Ishikawa, H., Shiroyama, K., Matsumoto, H., Fukumoto, K., J. Am. Chem. Soc., 99, 3461 (1977).