A SYNTHETIC APPROACH TO OLIVIN

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ABSTRACT

Olivin is the aglycone of olivomycin, a naturally occurring anti-tumor antibiotic. Synthesis of the aromatic portion of olivin was accomplished by using a new annellation procedure whereby 3-methyl-6,8-dimethoxy-1H-2-benzopyran-1-one was condensed with the lithium enolate of ethyl acetate to yield ethyl 1-hydroxy-6,8-dimethoxy-3-methyl-2-naphthoate.

The ortho relationship of the methyl and carboethoxy groups in the naphthoate was exploited in building the non-aromatic ring of olivin. Cycloaddition of maleic anhydride to dienes generated photochemically from 2-methylnaphthoyl nitriles failed. Base promoted condensation of triethyl 1,1,2-ethanetricarboxylate with ethyl 5(or 7)-bromo-1,6,8-trimethoxy-3-bromomethyl-2-naphthoate, generated the tricyclic anthracenone skeleton characteristic of olivin. However, the subsequent steps of hydrolysis and decarboxylation were not successful. The introduction of the side-chain was effected on a model substrate through the use of the lithium enolate of 2-propylidene-1,3-dithiane as a nucleophilic "acyl anion" equivalent.

INTRODUCTION

Scientists have in recent years intensified the search for
compounds having cancerostatic activity in the hope of finding drugs
that combine high therapeutic efficacy with low toxicity. At the
present time much interest is focused on a broad range of antitumor
antibiotics characterized by the combination of a polynuclear aromatic
skeleton with one or more carbohydrate chains. Among these are the
olivomycins and the chromomycins:[1a,1b]

OMe OH H Me
RO$_1$ 3 1' 2' 3' 4'
R 1 2 OR$_2$
OH OH O H OH
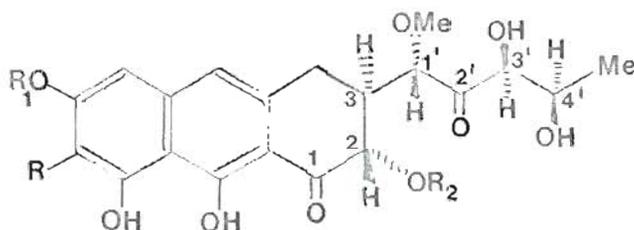
(1a) R_1 and R_2 = carbohydrate chains

     R = H or Me

(1b) R = R_1 = R_2 = H (olivin)

(1c) R = Me, R_1 = R_2 = H (chromomycinone)

These compounds are aureolic acid analogs whose structures were
elucidated independently in Japan,[2] and Russia.[3,4] Since publication
of the review article by Gause[5] (1965), these drugs have been under
intensive clinical study and have found widespread medical use in the

two countries mentioned. The most comprehensive structural work on the olivomycin antibiotics was reported by Berlin, Esipov, et al.[3] in 1966. These authors separated the mixture of antibiotics produced by Streptomyces olivoreticuli into the individual components: olivomycins A, B, C, and D. Hydrolysis of each component and analysis of the products obtained, showed that these substances possessed the same condensed carbocyclic portion but that they were different in their carbohydrate moieties. The same authors have also shown[3] that the absolute configuration of the five asymmetric centers of the olivomycin aglycone is: 2S, 3R, 1'S, 3'S, 4'R, thereby completely elucidating the structure of these antibiotics.

Recognition of olivomycin's efficacy in the treatment of several types of cancers, its relative unavailability from natural sources and the lack of structure-activity correlation studies, spurred our interest in synthetic approaches. Studies directed toward the development of a synthesis of olivin (1b), the aglycone portion of olivomycin, are the subject of this thesis.

SYNTHETIC STRATEGY

The olivin molecule (1b), can be conceptually separated into three parts: 1) an aromatic portion, 2) an alicyclic ring, and 3) a highly functionalized side chain. Our projected synthesis of olivin makes use of this conceptual division and permits the synthetic task to be divided into three smaller ones: the construction of the naphthalene system, the building of the alicyclic ring and the introduction of the side chain.

Viewing olivin (1b) as principally a naphthalene system upon which additional molecular framework is built, we decided to start its synthesis with the construction of an appropriately functionalized aromatic portion. To this portion we would then add, in a second stage, the alicyclic ring; finally, in a third stage, we would attach the side chain to the alicyclic ring.

CONSTRUCTION OF THE AROMATIC SYSTEM

For the synthesis of olivin and of many other natural products of similar structure, a method was needed that allowed the building of linear polynuclear aromatic skeletons in a simple and efficient way. Such a method would constitute a convenient entry into syntheses of numerous classes of biologically active compounds like the chromomycins and the rhodomycins.

To this end, a new aromatic annellation procedure (shown schematically below) which allows the regioselective construction of naphthalenes and anthracenes possessing 1-hydroxy-2-carboethoxy-3-methyl functionalization has been developed in our laboratory:[6]
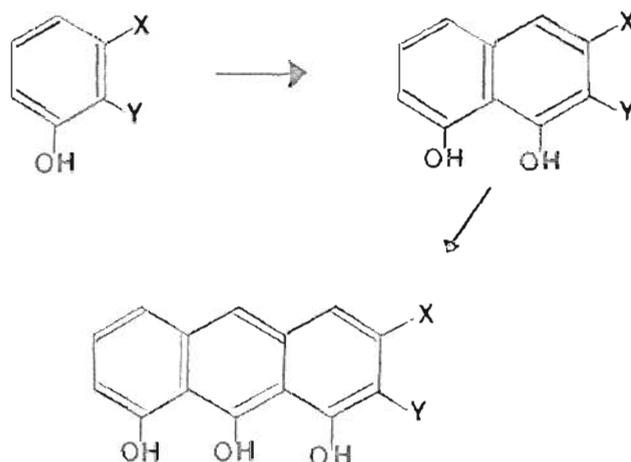
The procedure is direct, and represents at the present time the most efficient entry into systems of this kind.[7] The method permits the introduction of the "natural" hydroxylation pattern of olivin, and, importantly, it provides substitution patterns which make possible

the second stage of the synthesis: the building onto the aromatic
system of the alicyclic terminal ring of the olivin molecule.

For the synthesis of olivin, the specific starting material is
found in 2,4-dihydroxy-6-methylbenzoic acid (orsellinic acid, I) and
the X and Y substituents assume the identity of methyl and carboxyl
groups respectively:

I

II
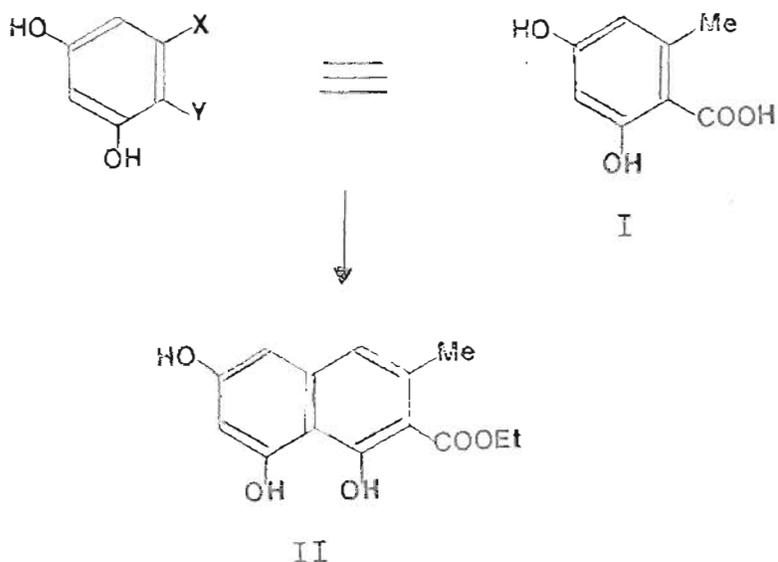
Schematic application of the annellation procedure to orsellinic acid
generates ethyl-1,6,8-trihydroxy-3-methyl-2-naphthoate (II). The X
and Y substituents appear once again on the newly built ring in the
form of a methyl and of an (esterified) carboxyl group. These sub-
stituents will be used in the second stage of the synthesis for the
attachment of the alicyclic ring.

The dimethyl ether of orsellinic acid (6) was prepared according to the method of Sonn[8] by the route shown below:
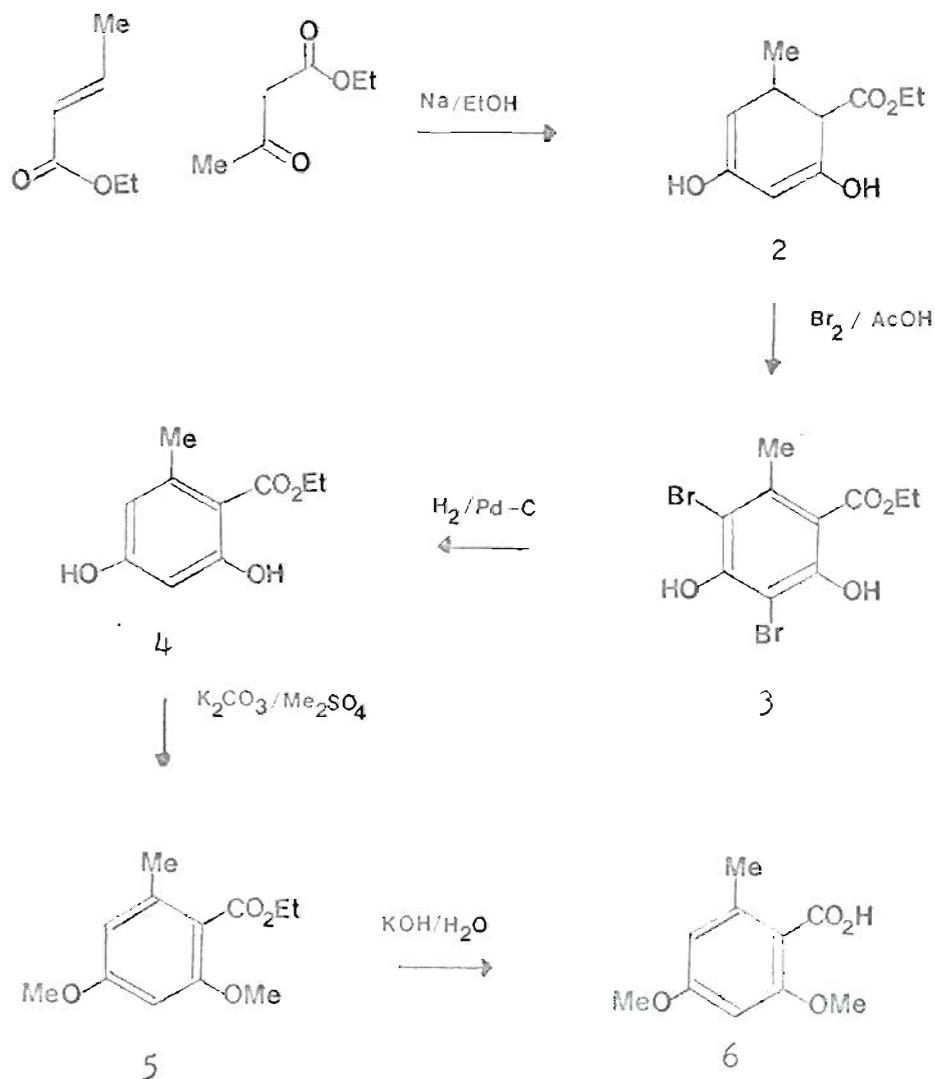
Condensation of ethyl acetoacetate with ethyl crotonate and aromatization of the ethyl dihydroorsellinate (2) thus formed, yielded dibromo compound 3. The dibromo compound was dehalogenated by hydrogenolysis[9] with palladium on carbon. The phenolic hydroxyls were methylated and

the ethyl ester was hydrolyzed to give 2,4-dimethoxy-6-methylbenzoic acid[10] (6) which constitutes the first aromatic ring in the olivin skeleton. It was used in the repetitive annellation sequence[6] to build the second aromatic ring.

Compound 6 was converted to 2-carboxy-3,5-dimethoxybenzeneacetic acid (7) by the method of Hauser.[11] Thus the doubly lithiated substrate was condensed with dimethyl carbonate at the benzylic position to give a methyl ester which upon hydrolytic workup yielded the homologous acid 7:
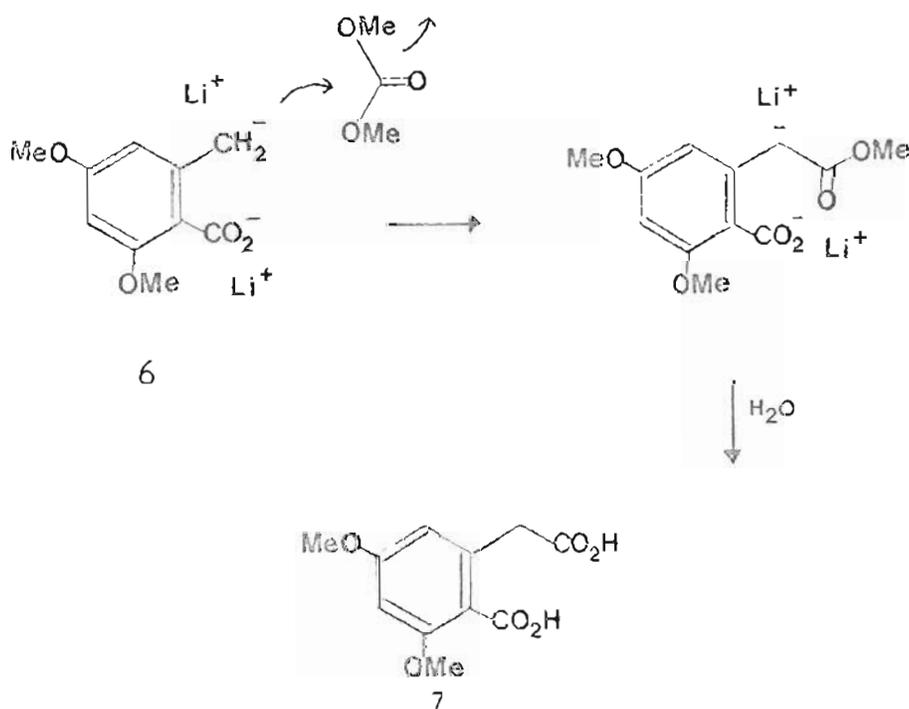
Homophthalic acid 7 was transformed into isocoumarin 10d via a three step sequence[12] with an overall yield of 70%. Thus, acylation of the benzylic position of 7, leads to ring closure through anhydride formation. Treatment of anhydride 8 with base accomplished ring opening and decarboxylation to yield the ketoacid 9 which underwent

acid catalyzed dehydrative ring closure to yield the desired 3-methyl-6,8-dimethoxy-1H-2-benzopyran-1-one (10d):
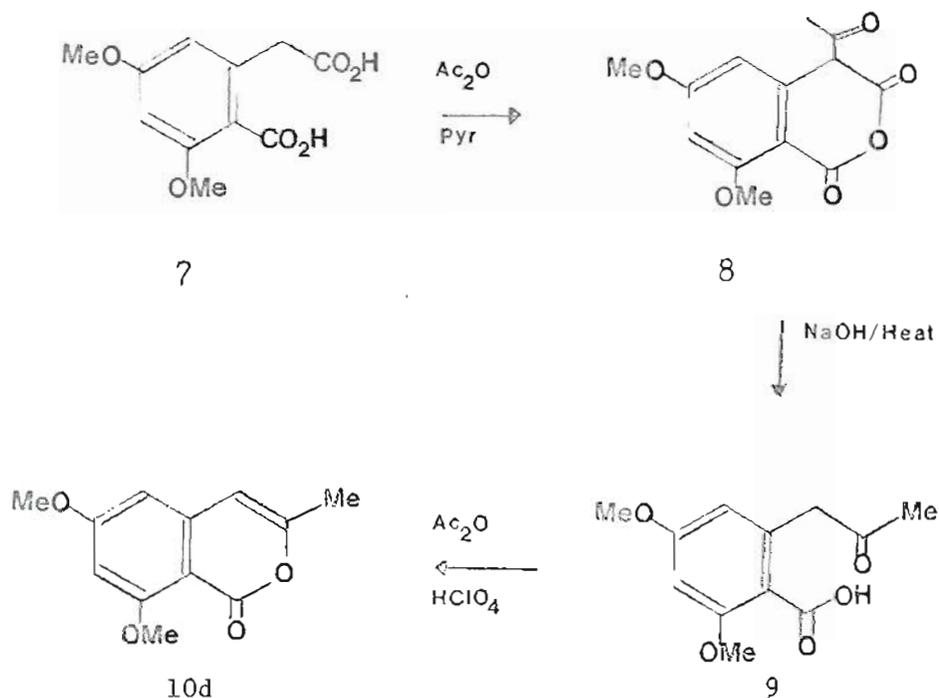
When isocoumarin 10d was reacted with the Reformatsky reagent derived from ethyl bromoacetate, demethylation of the 8-methoxyl group occurred and the expected ethyl 1-hydroxy-6,8-dimethoxy-3-methyl-2-naphthoate (11d) was obtained in only 24% yield. As an alternative to the Reformatsky reaction for accomplishing the desired transformation, the use of lithio ethyl acetate[13] was investigated. Isocoumarins 10a-d[6,14] upon condensation with the anion of ethyl acetate were successfully converted into naphthoates 11a-d in consistently high yields (87-93%):
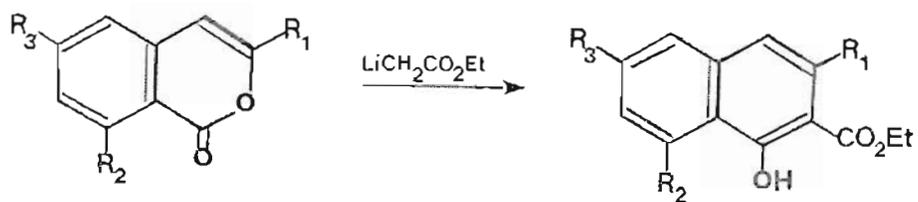
	R_1	R_2	R_3	% Yield
a.	H	H	H	93
b.	CH_3	H	H	92
c.	CH_3	OCH_3	H	91
d.	CH_3	OCH_3	OCH_3	87

The phenolic hydroxyl of 11d was methylated to give ethyl 1,6,8-trimethoxy-3-methyl-2-naphthoate (11e) completing the first stage of our projected olivin synthesis and thus preparing the molecule for the addition of the aliphatic ring.

CONSTRUCTION OF THE ALICYCLIC RING

We investigated two possible routes for the synthesis of the aliphatic ring of the molecule: 1) a photochemical route and 2) a condensation route.

Photochemical Route:

The transformations we hoped to accomplish photochemically are illustrated in Figure 1. The process shown in Figure 1 is a Diels-Alder reaction of maleic anhydride with an enol photochemically generated from the naphthalene system. Photoenolization is one of the most studied and most efficient of photochemical reactions. Yang[15] first reported that some o-alkylbenzophenones underwent photochemical enolization on ultraviolet irradiation.

The phenomenon has been studied through techniques such as product trapping by dienophiles,[16] and deuterium exchange.[17] Recent studies[18,19] indicate that both photoenol isomers (Z and E) are formed from 2-methyl-benzophenone; however, the Z-photoenol undergoes rapid hydrogen transfer leading to reketonization. The E-photoenol has a longer lifetime and can be trapped with dienophiles (Figure 2). In a related study, Sammes et al.[20] investigated the possibility of using cycloadducts formed from reaction of photogenerated dienols with dienophiles in the synthesis of natural products. They have shown (Figure 3) that the benzoyl nitrile functionality does undergo the photoenolization reaction and that the photoenol generated can be trapped by dienophiles. The Diels-Alder
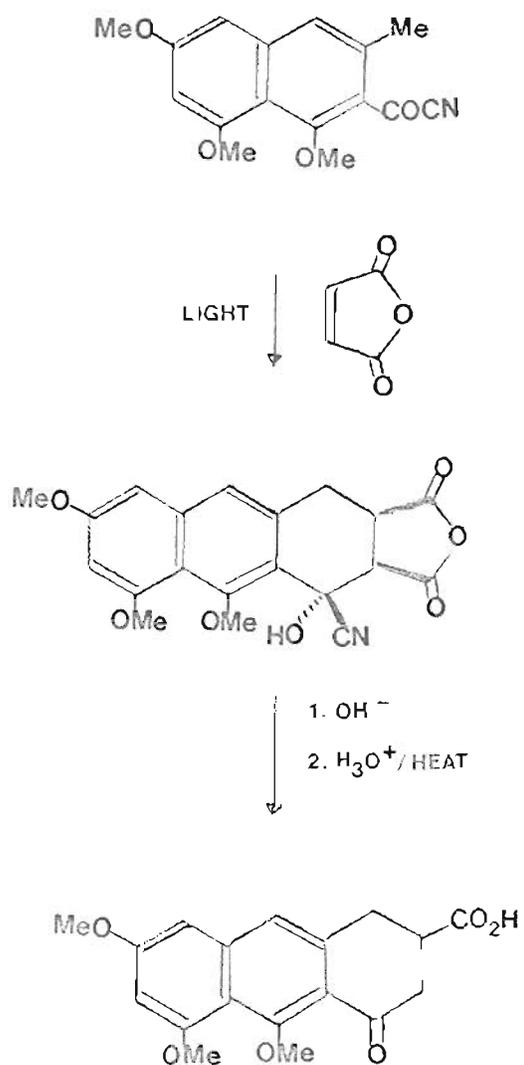
Figure 1
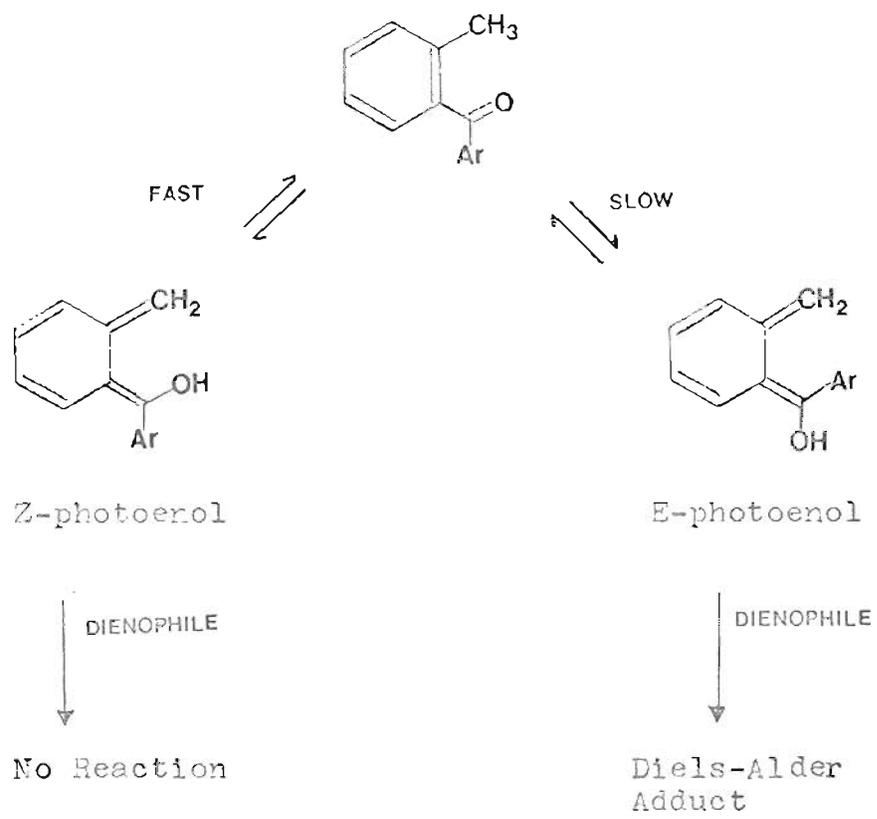
Figure 2
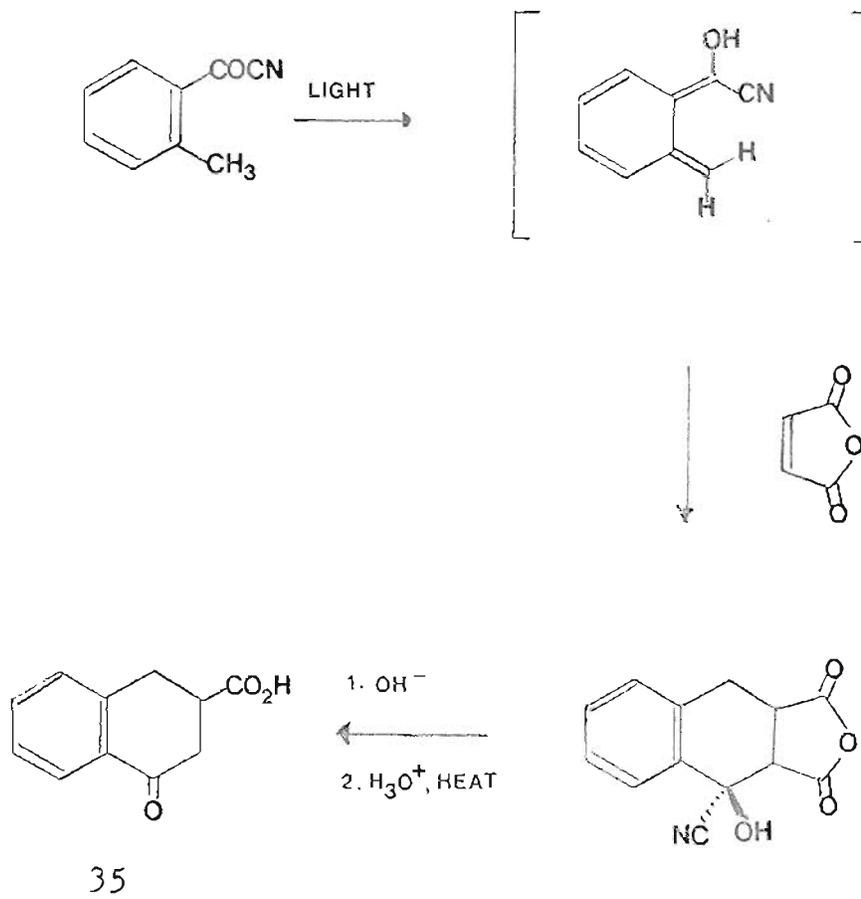
Figure 3

adduct with maleic anhydride is a cyanohydrin which, on basic hydrolysis and subsequent acidification, decarboxylates to give 1,2,3,4-tetrahydro-4-oxonaphthalene-2-carboxylic acid (35).

To test the utility of this photochemical approach for building the aliphatic ring of olivin, we synthesized acyl nitriles 17, 24 and 31 and subjected them to irradiation in the presence of maleic anhydride:
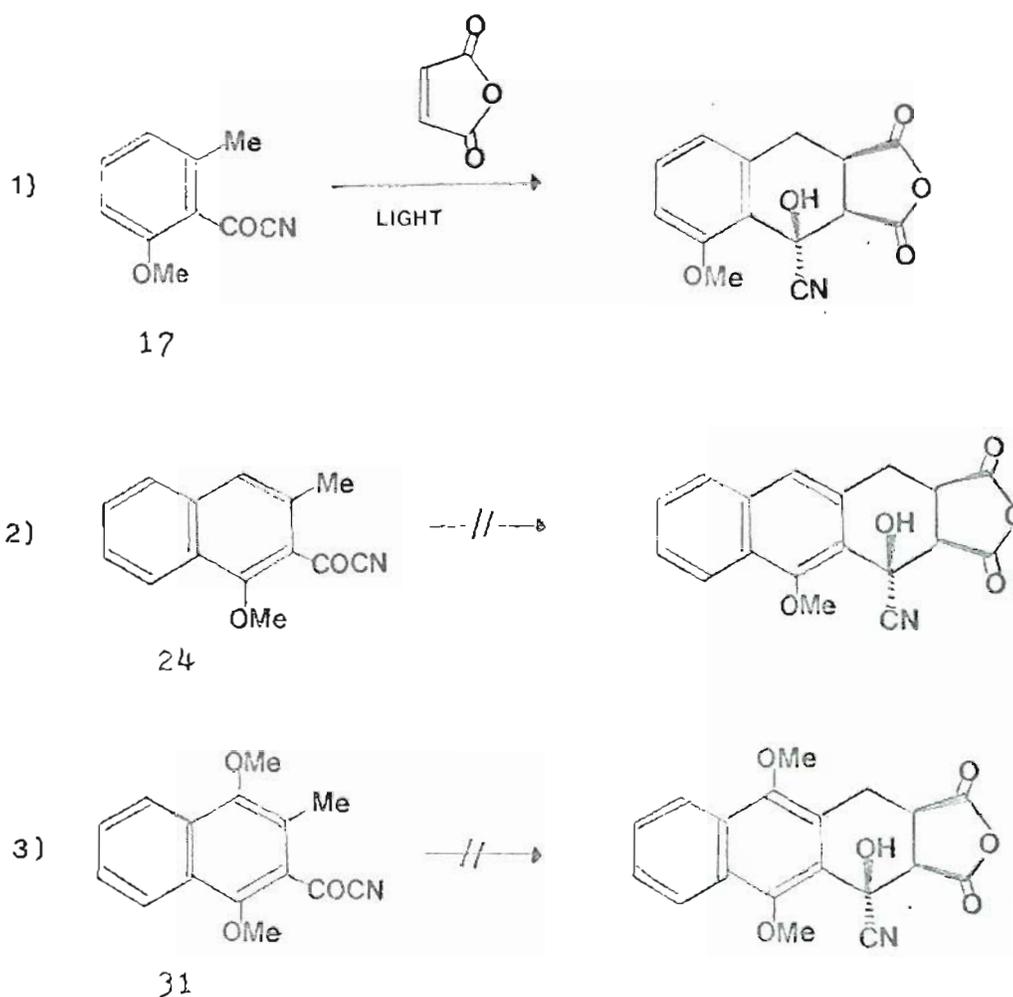
The single-ring compound 17 underwent photoenolization and was successfully trapped by maleic anhydride to give a 71% yield of the photoadduct. The bicyclic substrates 24 and 31 appeared to be

unreactive under all photochemical conditions and were recovered unchanged at the end of each trial. The photochemical inertness of naphthalene systems 24 and 31 prompted us to abandon this route.

Condensation Route:

Reaction of triethyl 1,1,2-ethanetricarboxylate with benzylic bromide 32, obtained by N-bromosuccinimide bromination of ethyl orthotoluate, in the presence of alkoxide (sodium or potassium t-butoxide in t-butanol) or hydroxide (potassium hydroxide in water/ethanol), effected alkylation producing 33; however, the second, condensation step did not occur. Ring closure to the keto triester 34 was attained by using two equivalents of sodium hydride in tetrahydrofuran at reflux.

In view of the possibility of a reverse Dieckmann reaction leading to ring opening, basic hydrolysis of triester 34 was not attempted. Hydrolysis and decarboxylation of 34 under acidic conditions was accomplished readily. When 34, in a mixture of acetic acid, hydrochloric acid and water (3:1:1) was heated on a steam bath for three days, keto-acid 35 was consistently obtained in yields of 80-85%. Less drastic conditions of time and temperature or absence of concentrated hydrochloric acid did not accomplish the hydrolysis (Figure 4).

In an attempt to prepare the necessary benzylic bromo compound in the naphthalene series leading to olivin, ethyl 1,6,8-trimethoxy-3-methyl-2-naphthoate (11e), was treated with one equivalent of N-bromosuccinimide; however only nuclear bromination occurred. The use of
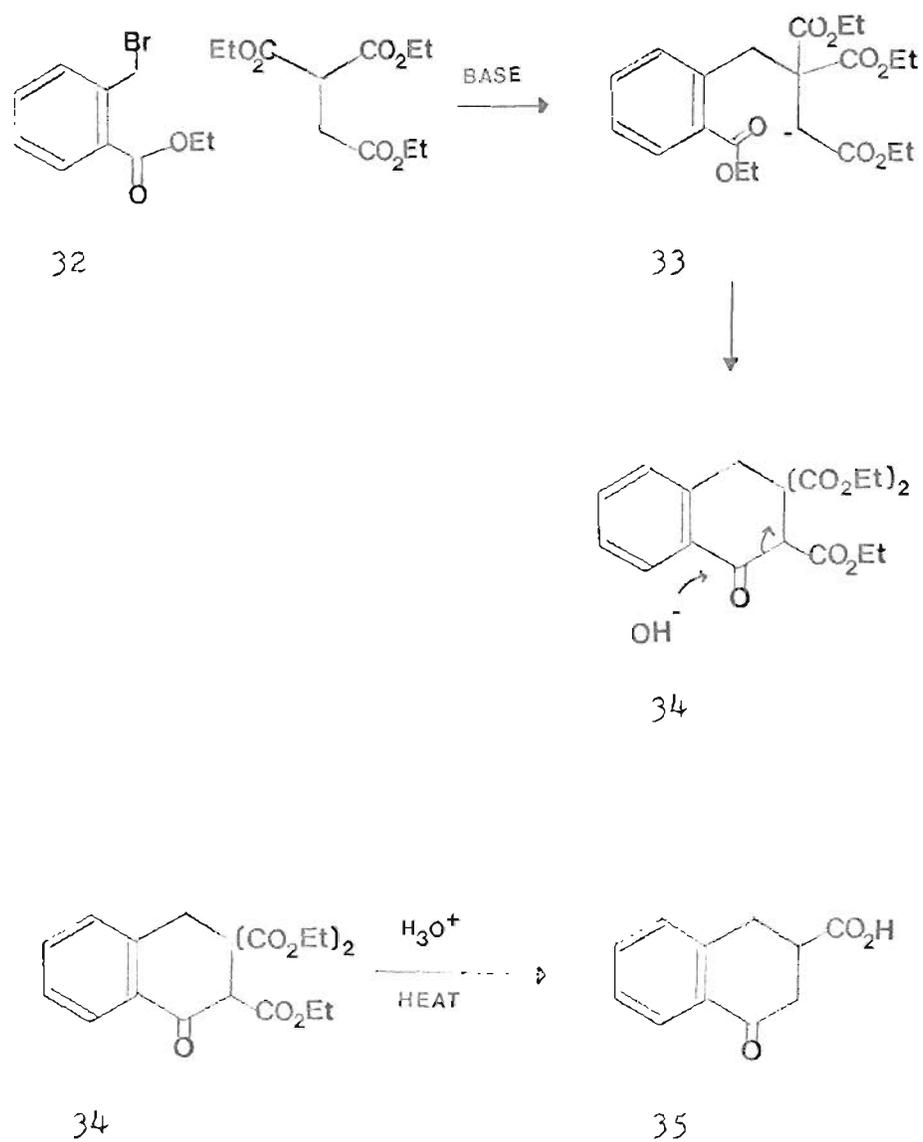
Figure 4

two equivalents of the brominating reagent resulted in complex reaction mixtures from which only low yields of a benzylic bromide could be obtained. The reactive naphthalene nucleus of 11e was therefore "protected" as its monobromo compound by titration with bromine at room temperature:

11e   46
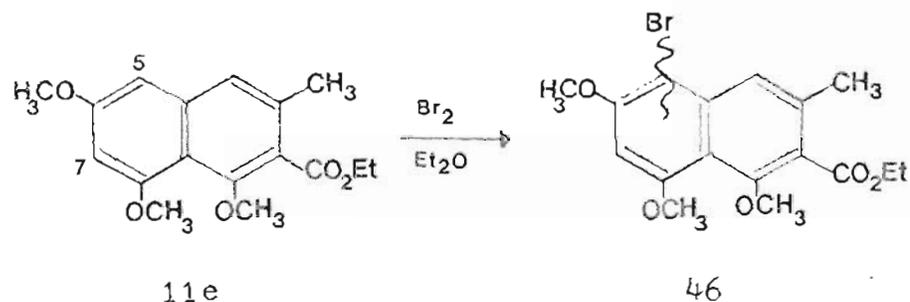
A mass spectrum of the resulting product (46) established the expected composition. An NMR spectrum did not permit the position of bromination (either position 5 or 7) to be definitely assigned. Compound 46 reacted cleanly with one equivalent of N-bromosuccinimide to give benzylic bromide 47:

47
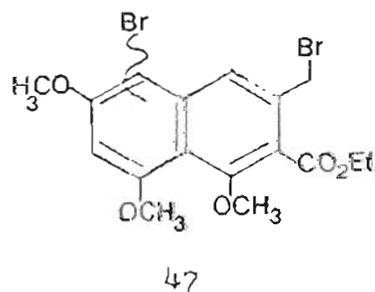
Dibromo compound 47 was condensed with ethyl 1,1,2-ethanetricarboxylate in the presence of excess sodium hydride in tetrahydrofuran to produce 48:

48
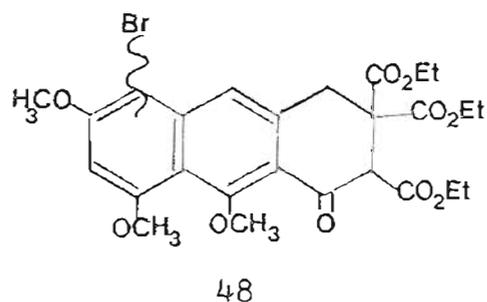
Attempts to hydrolize keto triester 48 under either acidic or basic conditions resulted in its partial or total destruction and did not yield the desired keto acid. In order to avoid the harsh conditions required to hydrolize triethyl ester 48, an alternative route was selected.

III

NaH/THF

49
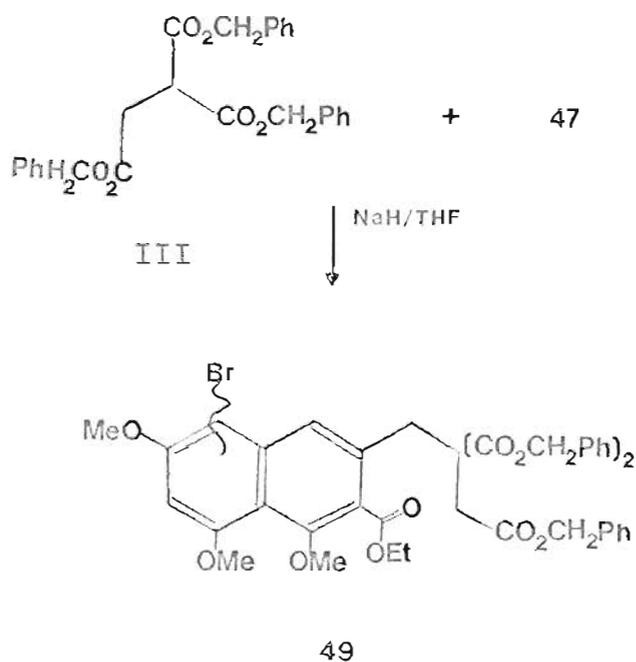
Transesterification[21] of ethyl 1,1,2-ethane tricarboxylate with benzyl alcohol yielded benzyl triester III which on reaction with di-bromo compound 47 gave rise to the alkylation product ethyl 5(or 7)-

bromo-1,6,8-trimethoxy-3-(3,3-benzyloxy-1-butylbenzoyl)-2-naphthoate
(49). Base induced cyclization of 49 at room temperature by means of
potassium t-butoxide in t-butanol or with sodium hydride in tetrahydro-
furan, failed. When the cyclization was attempted at a higher temperature
(60°C), thin layer chromatographic analysis revealed a very complex
reaction mixture from which no cyclized product could be isolated.

If cyclization of 49 should prove to be possible, generation of
the desired aliphatic ring is contemplated by hydrogenolysis of the
benzyl ester moieties and of the nuclear bromine atom in the cyclized
product, followed by thermal decarboxylation:
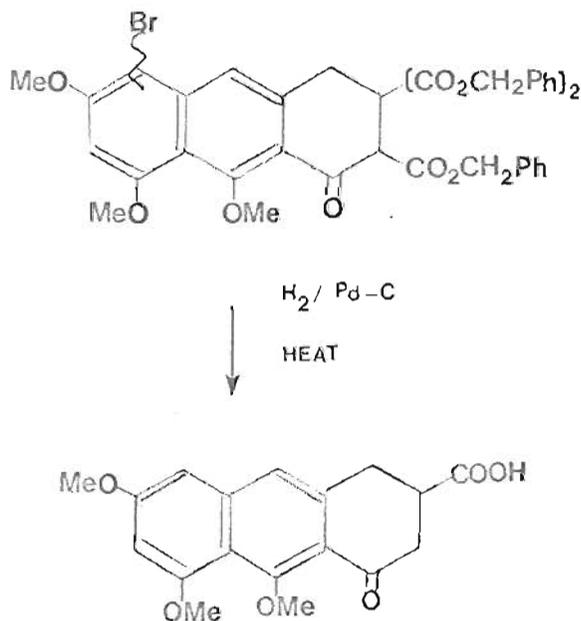
CONSTRUCTION AND ATTACHMENT OF THE FUNCTIONALIZED SIDE CHAIN

The plan successfully followed for the introduction of the five-carbon side chain is shown in Figure 5.
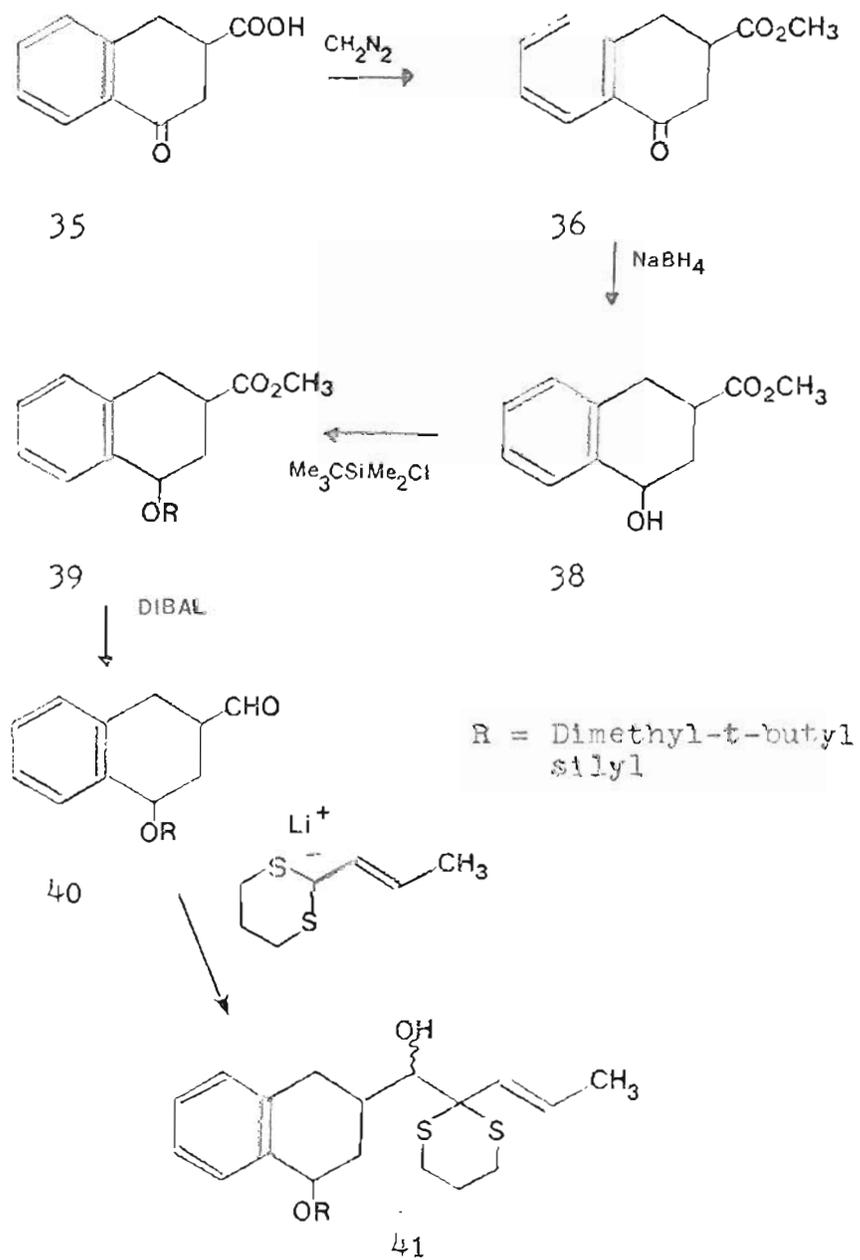
Figure 5

1,2,3,4-tetrahydro-4-oxonaphthalene-2-carboxylic acid (35), obtained by the condensation-hydrolysis route, was used as a model substrate to study the attachment of the side chain on the aliphatic ring of olivin.

After esterification of ketoacid 35 with diazomethane, the ketone function of the resulting ketoester 36 was selectively reduced[22] with sodium borohydride to the corresponding hydroxy compound 38. The hydroxyl group was protected as its t-butyldimethylsilyl ether[23] 39 and the ester was reduced with diisobutylaluminum hydride[24a,24b] to yield aldehyde 40. In an alternative, potentially shorter protection scheme, the ethylene ketal 37 was formed successfully from 36 (ethylene glycol, p-toluensulfonic acid, trimethyl orthoformate),[25] but the ketal proved to be too labile for chromatographic purification. Condensation of aldehyde 40 with the ketene thioacetal 45[26] derived from propionaldehyde and 1,3-dithiane,[27] accomplished in one step the introduction of a highly functionalized side-chain and the generation of the desired secondary alcohol. While two epimeric alcohols 41 were formed in an approximately 2:1 ratio from attack by the nucleophile on the two faces of aldehyde 40, only a single (E) double bond isomer was detected (NMR).

After introduction of the side chain, the feasibility of some further synthetic steps was proved and for all steps optimum reaction conditions were sought:
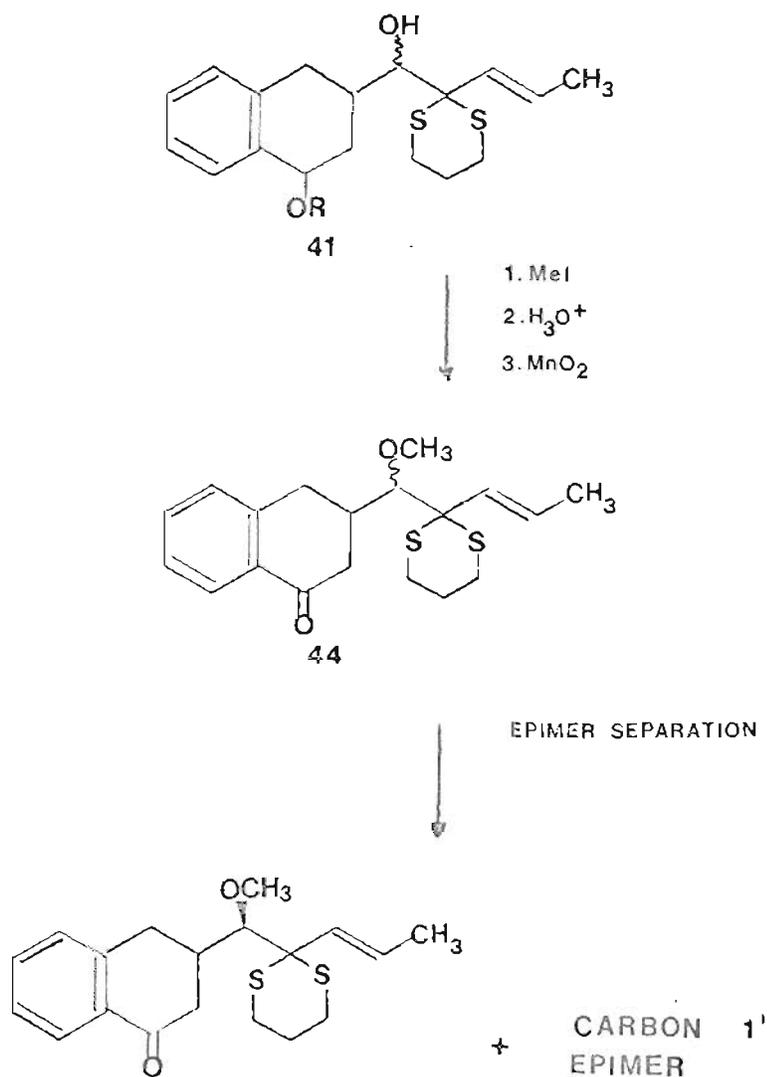
The mixture of epimeric alcohols 41 was methylated at ice bath temperature with sodium hydride and methyl iodide in the presence of hexamethylphosphoric triamide to generate methyl ethers 42. The silyl protective group of compounds 42 was smoothly removed by stirring in acetic acid, tetrahydrofuran, water (3:1:1) at 40°C for two days. Activated manganese dioxide[28] cleanly oxidized the benzylic alcohols 43 to the ketones 44. At this point the two epimeric methyl ethers 44 were separated by column chromatography on silica gel.

After removal of the thioketal, two additional steps can be envisaged to lead to a molecule whose aliphatic portion is identical to that of olivin:
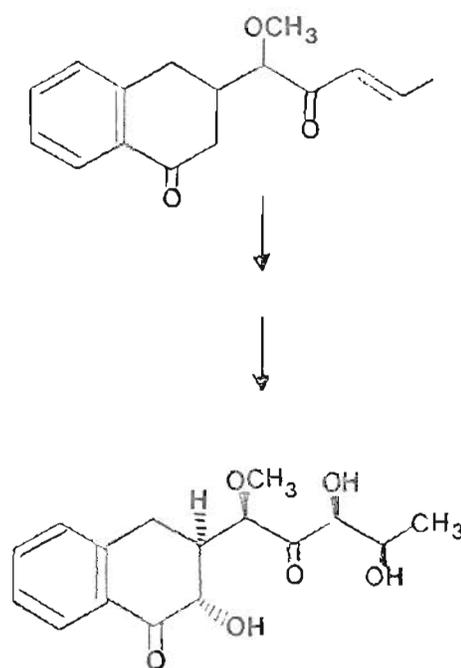
These two steps are: 1) a cis-hydroxylation of an olefin,[29] and 2) an alpha-hydroxylation of a ketone.[30]

SUMMARY

A new reaction sequence for the synthesis of olivin is presented
and its feasibility is investigated. The proposed synthetic scheme
consists of three stages: 1) construction of the aromatic portion,
2) attachment of the alicyclic ring, and 3) introduction of the side
chain.

The construction of the aromatic portion was accomplished by
using a modification of a new ring-building procedure developed entire-
ly in our laboratory. This modification (a wholly original contribution
of this thesis) makes available ethyl 1-hydroxy-6,8-dimethoxy-3-
methyl-2-naphthoate (the aromatic portion of the olivin skeleton) in
high yield.

The attachment of the alicyclic ring onto the pre-assembled naphtha-
lene nucleus was to be accomplished via a one-step photochemical cyclo-
addition, but this idea was abandoned when experiments showed that approp-
riately substituted (model) naphthalene compounds did not undergo the
photoreaction. An alternative method for the construction of the ali-
cyclic ring was then developed, in which triethyl 1,1,2-ethanetricarboxy-
late was condensed with an appropriately functionalized naphthalene
system in a one-step ring forming reaction. Although this method suc-
cessfully provided the desired alicyclic ring it proved to be trouble-
some in the subsequent required hydrolytic step.

In the construction and attachment of the functionalized side
chain, use was made of the concept of nucleophilic acylation. The

side chain was assembled and delivered in the form of a ketene thio-
acetal, a nucleophilic "acyl anion" equivalent. This method permitted
the introduction of a four carbon unit in a single step and at the same
time established the correct oxidation state at every carbon atom in
the chain.

EXPERIMENTAL SECTION

NMR spectra were taken on a Varian HA-100 spectrometer and are expressed in δ units. Tetramethylsilane (TMS) was employed as the internal standard. Mass spectra were obtained with CEC DuPont Model 21-110B or DuPont Model 21-491B spectrometers operated at 70 eV. Infrared spectra were obtained with a Perkin-Elmer 337 spectrophotometer. Melting points were determined on a Kofler hot stage microscope and are uncorrected. Thin layer chromatography was done on precoated TLC plates (E. Merck, silica-gel 60 F-254).

Ethyl 2-methyl-4,6-dioxocyclohexanecarboxylate (2).[8]

The procedure described by Sonn[8] was followed. Ethyl acetoacetate (140 g, 1.08 mol) was added to a stirred solution of sodium (23 g, 1 mol) in ethanol (300 mL) under nitrogen. After 15 minutes ethyl crotonate (115 g, 1.01 mol) was added. The reaction mixture was refluxed for five hours, cooled to 0°C and the sodium salt filtered and washed thoroughly with dry ether. The salt was dissolved in 350 mL of water and acidified with cold, concentrated hydrochloric acid. The precipitated product was isolated from the cold mixture by filtration and washed three times with ice water to yield 68 g (35%) of 2 as a white powder, m.p. 89-90°C (lit.[31] m.p. 89-90°C).

Ethyl 3,5-dibromo-2,4-dihydroxy-6-methylbenzoate (3).[8]

Bromine (176 g, 1.09 mol) in acetic acid (60 mL) was added drop-
wise to a stirred solution of ethyl 2-methyl-4,6-dioxocyclohexanecarbox-
ylate (2) (68 g, 0.344 mol) in acetic acid (180 mL) at a rate such that
the temperature did not exceed 40-45°C.

Upon completion of the addition, the slurry which had formed was
stirred for 1/2 hour and then heated on the steam bath until evolution
of hydrogen bromide ceased (circa 12 hours). The mixture was cooled and
1 liter of water was added. The precipitated solid was isolated by
suction filtration and washed well with ice water. After recrystal-
lization from ethanol, there were obtained 115 g (95%) of 3 as white
crystals, m.p. 142-144°C (lit.[32] m.p. 142-144°C).

Ethyl 2,4-dihydroxy-6-methylbenzoate (4).[8]

Ethyl 3,5-dibromo-2,4-dihydroxy-6-methylbenzoate (3), (20 g,
0.057 mol) dissolved in 1N sodium hydroxide (170 mL) was hydrogenated
over palladium on charcoal (0.5 g, 10%) at 40 psi until hydrogen uptake
ceased (2.5 hrs.). The solution was filtered through celite into 6N
cold hydrochloric acid to precipitate the product. The solid, isolated
by filtration, was dissolved in ethyl acetate, washed with water and
dried ($MgSO_4$) to give, on crystallization from ethanol, 9.15 g (87%) of
4 as a white powder, m.p. 131-132°C (lit.[8] m.p. 131-132°C); NMR ($CDCl_3$) δ
11.86 (s, 1, OH), 6.22 (AB quartet, J_{AB} = 4 Hz, 2, aromatic), 5.50
(broad s, 1, OH), 4.35 (q, J = 8 Hz, 2, OCH_2), 2.49 (s, 3, CH_3), 1.39
(t, J = 8 Hz, 3, CH_3).

Ethyl 2,4-dimethoxy-6-methylbenzoate (5).

Ethyl 2,4-dihydroxy-6-methylbenzoate (4), (55.3 g, 0.282 mol), dimethylsulfate (107 g, 0.846 mol) and potassium carbonate (156 g, 1.13 mol), were stirred under nitrogen in acetone (400 mL) at reflux for two days. The solids were removed by filtration and the solvent was evaporated to give an oil. Excess dimethylsulfate was removed by dissolving the oil in ethyl ether and treating the solution with triethylamine. The cloudy solution that formed was washed successively with water, 3N hydrochloric acid and again with water. The solution was dried (MgSO$_4$) and the ether evaporated to give 63 g (100%) of 5 as a colorless oil homogeneous by TLC; NMR (CDCl$_3$) δ 6.30 (broad s, 2, aromatic), 4.35 (q, J = 8 Hz, 2, OCH$_2$), 3.78 (s, 6, OCH$_3$), 2.29 (s, 3, CH$_3$), 1.33 (t, J = 8 Hz, 3, CH$_3$).

2,4-dimethoxy-6-methylbenzoic acid (6).[10]

Ethyl 2,4-dimethoxy-6-methylbenzoate (5), (63 g, 0.281 mol) and potassium hydroxide (100 g, 1 mol), dissolved in dimethylsulfoxide (500 mL) and water (160 mL) were heated on the steam bath with stirring for 12 hours. The chilled solution was acidified with cold, concentrated hydrochloric acid. The resulting white crystals of carboxylic acid 6 were isolated by filtration and weighed 47 g (85.3%); m.p. 144-146°C, (lit.[10] m.p. 140°C), NRM (CDCl$_3$) δ 9.50 (br, 1, COOH), 6.45 (br, 2, aryl), 3.82 (s, 3, OCH$_3$), 3.81 (s, 3, OCH$_3$), 2.35 (s, 3, CH$_3$).

2-carboxy-3,5-dimethoxybenzeneacetic acid (7).[33]

To a cold (0°C) solution of diisopropylamine (32.1 g, 0.318 mol) in tetrahydrofuran (100 mL) stirred under nitrogen was added n-butyl lithium (200 mL, 1.6 M, 0.318 mol). The solution was cooled to -78°C and 2,4-dimethoxy-6-methylbenzoic acid (6), (15.64 g, 0.079 mol) was added. The cooling bath was removed and dimethylcarbonate (14.5 g, 0.159 mol) was added rapidly. The mixture was stirred for 4 hours and then water (130 mL) was added. After stirring overnight, the solution was concentrated under vacuum, acidified with concentrated hydrochloric acid and refrigerated. The homophthalic acid 7 which precipitated was isolated by filtration and washed with cold water. After recrystallization from hexanes/acetone there was obtained 18.19 g (95% yield): m.p. 168-172°C, (lit.[33] m.p. 172-173°C), NMR (acetone-d_6) δ 5.59 (s, 2, aromatic), 3.90 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 3.80 (s, 2, benzyl).

3-methyl-6,8-dimethoxy-1H-2-benzopyran-1-one (10d).[34]

To a stirred mixture of acetic anhydride (10 mL) and pyridine (1 mL), was added 2-carboxy-3,5-dimethoxybenzeneacetic acid (7), (2 g, 8.34 mmol). Ether was added to facilitate stirring the thick precipitate which formed. Stirring was continued for two hours at which time the solids were isolated by filtration and washed with ether. The solid material was covered with water (30 mL) and heated with stirring on the steam bath while a 10% sodium hydroxide solution was added dropwise until the reaction mixture was basic (pH = 10). Heating was continued for one hour, and the hot solution was cautiously acidified with

stirred at room temperature for 48 hours. The tetrahydrofuran was evaporated at reduced pressure, the residue was taken up in ether (100 mL) and the solution washed with water (2 x 25 mL). The solvent was dried ($MgSO_4$), then evaporated to give impure naphthoates 11a-d. Pure naphthoates were obtained by slug chromatography (silica gel, 30 g, CH_2Cl_2).

Ethyl 1-hydroxy-2-naphthoate (11a).[35]

Yield: 93%, m.p. 48-49°C, (lit.[35] m.p 48-49.5°C), NMR ($CDCl_3$) δ 12.04 (s, 1, OH), 8.50-8.35 (m, 1, aromatic), 7.79-7.17 (m, 5, aromatic), 4.42 (q, J = 8 Hz, 2, OCH_2), 1.42 (t, J = 8 Hz, 3, CH_3).

Ethyl 1-hydroxy-3-methyl-2-naphthoate (11b).[35]

Yield: 92%, m.p. 58-59°C, (lit.[35] m.p. 56-59°C), NMR (CCl_4) δ 12.72 (s, 1, OH), 8.23 (m, 1, aromatic), 7.44-7.15 (m, 3, aromatic), 6.80 (broad s, 1, aromatic), 4.23 (q, J = 8 Hz, 2, OCH_2), 2.43 (s, 3, CH_3), 1.29 (t, J = 8 Hz, 3, CH_3).

Ethyl 1-hydroxy-8-methoxy-3-methyl-2-naphthoate (11c).[6,14]

Yield: 91%, m.p. 59-60°C, (lit.[6,14] m.p. 59°C), NMR ($CDCl_3$) δ 10.24 (s, 1, OH), 7.25-7.15 (m, 2, aromatic), 6.99 (s, 1, aromatic), 6.59 (m, 1, aromatic), 4.42 (q, J = 8 Hz, 2, OCH_2), 3.88 (s, 3, OCH_3), 2.40 (s, 3, CH_3), 1.40 (t, J = 8 Hz, 3, CH_3).

Ethyl 1-hydroxy-6,8-dimethoxy-3-methyl-2-naphthoate (11d).[14]

Yield: 87%, m.p. 68-70°C, (lit.[14] m.p. 68-70°C), NMR (CDCl$_3$) δ
10.76 (s, 1, OH), 6.88 (s, 1, aromatic), 6.51 and 6.32 (AB quartet,
J$_{AB}$ = 2 Hz, 2, aromatic), 4.38 (q, J = 8 Hz, 2, OCH$_2$), 3.90 (s, 3,
OCH$_3$), 3.80 (s, 3, OCH$_3$), 2.42 (s, 1, CH$_3$), 1.40 (t, J = 8 Hz, 3,
CH$_3$).

Ethyl 1,6,8-trimethoxy-3-methyl-2-naphthoate (11e).[14]

To a stirred solution of naphthoate 11d (1.65 g, 5.69 mmol)
in acetone under nitrogen, were added dimethylsulfate (2.15 g, 17.1 mmol)
and potassium carbonate (2.36 g, 17.1 mmol). The mixture was stirred
at reflux for 24 hours, the solids were removed by filtration and the
solvent was evaporated to give an oil. Excess dimethylsulfate was re-
moved by dissolving the oil in ethyl ether and treating the solution
with triethylamine. The cloudy solution that formed was washed suc-
cessively with water, 3N hydrochloric acid and again with water. The
solution was dried (MgSO$_4$) and the ether evaporated to give 1.68 g
(97%) of 11e as a pale greenish oil, NMR (CCl$_4$) δ 7.13 (broad s, 1,
aromatic), 6.52 and 6.38 (AB quartet, J$_{AB}$ = 2 Hz, 2, aromatic), 4.38
(q, J = 8 Hz, 2, OCH$_2$), 3.93 (s, 3, OCH$_3$), 3.82 (s, 3, OCH$_3$), 3.79
(s, 3, OCH$_3$), 2.38 (s, 3, CH$_3$), 1.42 (t, J = 8 Hz, 3, CH$_3$).

Ethyl 5(or 7)-bromo-1,6,8-trimethoxy-3-methyl-2-naphthoate (46).

To a solution of 30 mg (0.01 mmol) of naphthoate 11e in ethyl
ether (10 mL), was added bromine dropwise until the brown color no

longer faded. Evaporation of the ether in vacuo gave 35 mg (93%) of
yellowish solid homogeneous by TLC (5% EtOAc/CHCl₃). This material
was identified as compound 46 by its spectral data. NMR (CCl₄) δ
7.75 (broad s, 1, aromatic), 6.50 (s, 1, aromatic), 4.35 (quartet,
J = 8 Hz, 2, OCH₂), 3.91 (s, 6, OCH₃), 3.78 (s, 3, OCH₃), 2.41
(s, 3, CH₃), 1.42 (t, J = 8 Hz, 3, CH₃); mass spectrum m/e 382 (M⁺).

Ethyl 5(or 7)-bromo-1,6,8-trimethoxy-3-bromomethyl-2-naphthoate (47).

To a solution of 119 mg (0.311 mmol) of monobromo compound 46 in
carbon tetrachloride (10 mL), was added 55.4 mg (0.311 mmol) of N-
bromosuccinimide and the stirred mixture was irradiated under nitrogen
with a u.v. lamp for 30 minutes. The cold mixture was filtered and the
solvent was evaporated to give after slug chromatography (silica gel,
30 g, CHCl₃) 110 mg (77%) of 47 as a solid. NMR (CCl₄) δ 7.93 (broad s,
1, aromatic), 6.55 (broad s, 1, aromatic), 4.62 (s, 2, benzylic), 4.42
(quartet, J = 8 Hz, 2, CH₂), 3.95 (s, 3, OCH₃), 3.93 (s, 3, OCH₃), 3.79
(s, 3, OCH₃), 1.46 (t, J = 8 Hz, 3, CH₃).

2,3,3-tricarboethoxy-3,4-dihydro-5(or 7)-bromo-6,8,9-trimethoxy-
1(2H)-anthracenone (48).

Sodium hydride 0.192 g (4 mmol) was added to dry tetrahydrofuran
(10 mL) under nitrogen. To the stirred suspension, triethyl 1,1,2-
ethane tricarboxylate[36] (0.985 g, 4 mmol) was added at once (foaming!).
After 10 minutes the benzylic bromide 47, (1.44 g, 3.12 mmol) in tetra-
hydrofuran (2 mL) was added rapidly. One hour later a second equivalent
(0.192 g, 4 mmol) of sodium hydride was added. Stirring and reflux were

continued for 24 hours. The reaction was quenched with glacial acetic acid, the tetrahydrofuran was evaporated and the residue was taken up in ethyl acetate which was in turn washed with water. The ethyl acetate layer was dried over $MgSO_4$ and evaporated. The residual oil was purified by column chromatography (silica gel, 100 g, $CHCl_3$). There was obtained 1.64 g (91%) of 48 as an oil. NMR (CCl_4) δ 7.68 (broad s, 1, aromatic), 6.50 (broad s, 1, aromatic), 4.35-3.90 (m, 6, methylene), 3.98 (s, 3, OCH_3), 3.95 (s, 3, OCH_3), 3.81 (s, 3, OCH_3), 1.50-1.05 (m, 9, CH_3), mass spectrum m/e 582 (M^+).

Transesterification[21] of triethyl 1,1,2-ethane tricarboxylate to tribenzyl 1,1,2-ethane tricarboxylate (III).

Sodium (0.5 g) was dissolved in benzyl alcohol (15 mL) and pentane (30 mL). At this point a white, gelatinous precipitate had formed. Activated (400°C, 2 hours) 4Å molecular sieves (30 g of pellets) were added, followed immediately by 3 g (12.2 mmol) of triethyl 1,1,2-ethane tricarboxylate.[36] The mixture was stirred at room temperature for 4 hours at which time TLC analysis ($CHCl_3$) indicated completion of the reaction. After addition of glacial acetic acid (10 mL), the solids were removed by filtration through celite and the solution was concentrated under vacuum. The excess benzyl alcohol was removed by vacuum distillation (55°C, 1 mm), to give 3.9 g (74%) of tribenzyl 1,1,2-ethane tricarboxylate (III) as an oil: NMR (CCl_4) δ 7.22 (s, 5, aromatic), 7.20 (s, 10, aromatic), 5.09 (s, 4, benzylic), 5.02 (s, 2, benzylic), 3.85 (t, J = 8 Hz, 1, methine), 2.92 (d, J = 8 Hz, 2, methylene), mass spectrum m/e 432 (M^+).

Ethyl 5(or 7)-bromo-1,6,8-trimethoxy-3-(3,3-benzyloxy-1-butyl-
benzoyl)-2-naphthoate (49).

Sodium hydride (10 mg, 0.41 mmol) was added to dry tetrahydrofuran
(10 mL) under nitrogen. To the stirred suspension was added 13.7 mg
(0.032 mmol) of tribenzyl 1,1,2-ethane tricarboxylate (III) and 14.7 mg
(0.032 mmol) of dibromo compound 47. After 24 hours at room temperature
the reaction was quenched by the addition of glacial acetic acid (2 mL).
The mixture was evaporated to dryness and the residue was taken up in
ethyl acetate. The organic layer was washed with water and dried over
$MgSO_4$. Evaporation of the solvent followed by slug chromatography
yielded 10 mg (38%) of 49 as a yellow oil: NMR ($CDCl_3$) δ 7.81
(broad, s, 1, aromatic), 7.28 (s, 5, phenyl), 7.22 (s, 5, phenyl),
7.19 (s, 5, phenyl), 6.65 (broad s, 1, aromatic), 5.15 (s, 4, benzyl),
5.05 (s, 2, benzyl), 4.30 (quartet, J = 8 Hz, 2, OCH_2), 4.00 (s, 6, OCH_3),
3.81 (s, 3, OCH_3), 1.55-1.05 (m, 3, CH_3), mass spectrum m/e 812 (M^+).

Ethyl 6-methyl-3-cyclohexen-2-one carboxylate (12).[37]

To a stirred solution of sodium (1 g) in dry ethanol (400 mL)
under nitrogen was added ethyl acetoacetate (195 g, 1.5 mol), followed
after 10 minutes by crotonaldehyde (105 g, 1.5 mol). The resulting
mixture was stirred overnight and then dry hydrogen chloride was
bubbled into the solution for 45 minutes. The solution was kept over-
night at room temperature, then evaporated to give an oil which was
taken up in ether and washed several times with water. The reaction
was monitored by NMR (CCl_4) and was considered complete when the peak

at δ 2.18 had disappeared. Evaporation of the ether and distillation of the residue gave substituted cyclohexenone 12 (126 g, 46% yield) as a mixture of stereoisomers (b.p. 79-88°C, 0.8 mm), NMR (CCl₄) δ 7.08-6.82 (m, 1, vinyl), 6.18-5.82 (d, 1, vinyl), 4.19 (q, J = 8 Hz, 2, OCH₂), 3.23-2.10 (m, CH₂, CH), 1.29 (m, 3, CH₃), 1.08 (d, J = 8 Hz, 3, CH₃).

Ethyl 2-hydroxy-6-methylbenzoate (13).[38]

To cyclohexenone 12 (68.5 g, 0.377 mol) in carbon tetrachloride (280 mL) was added in a thin stream a solution of bromine (60 g, 0.37 mol) in acetic acid (375 mL). The reaction mixture was heated under reflux (nitrogen) for 24 hours. After cooling, water (500 mL) and methylene chloride (500 mL) were added to separate the layers. The carbon tetrachloride phase was washed repeatedly with water and sodium bicarbonate solution. Evaporation of the solvent and steam distillation of the residue gave after recrystallization from ethanol/water 53 g (78%) of 13, m.p. 40-41°C. NMR (CCl₄) δ 11.20 (br, 1, OH), 7.20 (t, J = 8 Hz, 1, aromatic), 6.75 (d, J = 8 Hz, 1, aromatic), 6.62 (d, J = 8 Hz, 1, aromatic), 4.41 (q, J = 8 Hz, 2, OCH₂), 2.53 (s, 3, CH₃), 1.48 (t, J = 8 Hz, 3, CH₃).

Ethyl 2-methoxy-6-methylbenzoate (14).

Phenol 13 (7 g, 39 mmol), dimethylsulfate (5.16 g, 41 mmol), potassium carbonate (5.66 g, 41 mmol) and acetone (250 mL) were stirred under nitrogen at reflux for 24 hours. The solids were removed by filtration and the solvent was evaporated to give an oil. Excess

dimethylsulfate was removed by dissolving the oil in ethyl ether and treating the solution with triethylamine. The cloudy solution that formed was washed successively with water, 3N hydrochloric acid and again with water. The solution was dried (MgSO$_4$) and the ether evaporated to give 7.56 g (100%) of 14 as an oil; NMR (CCl$_4$) δ 7.35-7.09 (m, 1, aromatic), 6.70 (d of d, J = 4 Hz, 2, aromatic), 4.33 (q, J = 8 Hz, 2, OCH$_2$), 3.83 (s, 3, OCH$_3$), 2.28 (s, 3, CH$_3$), 1.39 (t, J = 8 Hz, 3, CH$_3$).

2-methoxy-6-methylbenzoic acid (15).[39]

Ethyl 2-methoxy-6-methylbenzoate (14) (7.56 g, 39 mmol) was dissolved in dimethylsulfoxide (200 mL). Potassium hydroxide (14.5 g, 258 mmol) in water (20 mL) was added and the solution was heated on the steam bath overnight. The cool solution was poured into 3N hydrochloric acid and extracted with ether. After recrystallization from hot water/ethanol there were obtained 3.2 g (50%) of 15, m.p. 139-141°C (lit. m.p. 139°C), NMR (CCl$_4$) δ 9.50-9.00 (br, 1, COOH), 7.30 (m, 1, aromatic), 6.92-6.79 (m, 2, aromatic), 3.97 (s, 3, OCH$_3$), 2.52 (s, 3, CH$_3$).

2-methoxy-6-methylbenzoylcyanide (17).

2-methoxy-6-methylbenzoic acid (15) (3.9 g, 23.5 mmol) was heated under reflux (nitrogen) for two hours in thionyl chloride (20 mL). The thionyl chloride was evaporated at reduced pressure to give 4.3 g (98%) of the acyl chloride 16 as an oil: IR (neat) 1780 cm^{-1}. Acyl chloride 16 was added to a suspension of cuprous cyanide[40] (46.8 mmol) in acetonitrile (30 mL). The mixture was heated (nitrogen) under

reflux for two hours. After evaporation of the solvent and purification (silica gel, 100 g, benzene) there was obtained 2.5 g (61%) of nitrile 17, m.p. 54°C, IR (KBr), 2200 (CN), 1680 (C=O) cm^{-1}; NMR (CCl$_4$) δ 7.50 (t, J = 10 Hz, 1, aromatic), 6.90 (d, J = 10 Hz, 2, aromatic), 4.02 (s, 3, OCH$_3$), 2.48 (s, 3, CH$_3$); u.v. (MeOH) 224, 284, 350 nm.

1,2,3,4-tetrahydro-5-methoxy-4-oxonaphthalene-2-carboxylic acid (18).

A solution of 2-methoxy-6-methylbenzoylcyanide (17) (0.399 g, 2.28 mmol) and maleic anhydride (0.224 g, 2.28 mmol) in ethyl acetate (20 mL) was purged with nitrogen and heated under reflux. The solution under nitrogen was irradiated with a sun lamp for 5 days. The ethyl acetate was evaporated and the residue was taken up in benzene. Potassium carbonate (0.60 g) in water (15 mL) was added and the mixture was heated under reflux for 1 hour. Acidification with concentrated hydrochloric acid produced ketoacid 18 (0.25 g, 52%) in crystalline form, m.p. 175-180°C, NMR (DMSO-d$_6$) δ 10.15 (br, 1, COOH), 7.42 (t, J = 8 Hz, 1, aromatic), 6.85 (d, J = 8 Hz, 2, aromatic), 3.91 (s, 3, OCH$_3$), 3.35-2.85 (m, 5, CH$_2$); mass spectrum m/e 220 (M$^+$).

Ethyl 1-methoxy-3-methyl-2-naphthoate (21).

A vigorously stirred mixture of ethyl 1-hydroxy-3-methyl-2-naphthoate (11b) (3.95 g, 17.2 mmol), dimethylsulfate (2.27 g, 18.0 mmol) and anhydrous potassium carbonate (4.74 g, 34.4 mmol) in acetone (100 mL) was heated under reflux (nitrogen) for 1 day. After removing the solids by filtration, the solvent was evaporated to give an oil. Excess dimethylsulfate was removed by dissolving the oil in ether (20 mL) and

treating the solution with triethylamine (5 mL). The cloudy solution that formed was washed successively with water (3 x 20 mL), hydrochloric acid (3N, 20 mL) and water (20 mL). The solution was dried over $MgSO_4$ and the ether evaporated to give a quantitative yield (4.2 g) of 21 as a colorless oil. NMR (CCl_4) δ 7.99 (m, 1, aromatic), 7.65-7.21 (m, 4, aromatic), 4.35 (q, J = 8 Hz, 2, OCH_2), 3.95 (s, 3, OCH_3), 2.40 (s, 3, CH_3), 1.38 (t, J = 8 Hz, 3, CH_3).

1-methoxy-3-methyl-2-naphthoic acid (22).

To ethyl 1-methoxy-3-methyl-2-naphthoate (21) (4.2 g, 17.2 mmol) dissolved in dimethylsulfoxide (50 mL) was added potassium hydroxide (3.82 g, 68 mmol) in water (10 mL). The solution under nitrogen was heated on the steam bath for 4 hours, then stirred overnight. The cold solution was poured into 6N hydrochloric acid and the resultant crystal-line material was isolated by filtration. After recrystallization from benzene/petroleum ether there were obtained 3.20 g (86%) of 22, m.p. 95-97°C, NMR (CCl_4) δ 12.43 (s, 1, COOH), 8.08 (m, 1, aromatic), 7.72-7.25 (m, 4, aromatic), 4.10 (s, 3, OCH_3), 2.59 (s, 3, CH_3).

1-methoxy-3-methyl-2-naphthoylnitrile (24).

1-methoxy-3-methyl-2-naphthoic acid (22) (2.56 g, 11.9 mmol) and thionyl chloride (5.65 g, 47.6 mmol) in benzene (40 mL) were heated under reflux (nitrogen) for 7 hours. The benzene and the thionyl chloride were evaporated under reduced pressure to give 2.3 g of acyl chloride 23, IR (neat) 1780 cm^{-1}. Acyl chloride 23 was added to a stirred suspension of cuprous cyanide[40] (2.13 g, 23.8 mmol) in

acetonitrile (30 mL) under nitrogen. The reaction soon became homogeneous and the color changed from light brown to yellow green. Stirring was continued for a total of 6 hours. The acetonitrile was evaporated and the residue on treatment with ether gave a solid which was removed by filtration. Evaporation of the solvent yielded a greenish oil which, after purification (silica gel, 30 g, benzene), gave 24 as yellow fluorescent crystals (0.8 g, 30% yield), m.p. 88-89°C, IR (neat) 2220, 1680 cm^{-1}; u.v. (MeOH) 228, 270, 312 nm.

2-sodium-2-methyl-1,3-indandione (25).[41]

To a dispersion of sodium hydride (24 g, 50% in mineral oil) in anhydrous benzene (500 mL) was slowly added a mixture of 3-pentanone (41 g, 0.47 mol) and dimethylphthalate (100 g, 0.51 mol). The mixture was heated under reflux for 15 hours; 2-sodium-2-methyl-1,3-indandione (25) precipitated on cooling as a deep red solid. It was collected and dried under vacuum.

Ethyl 2-methyl-1,3-indandione-2-acetate (26).[42]

To 2-sodium-2-methyl-1,3-indandione (25) (14.8 g, 81.3 mmol) suspended in ethanol (250 mL) was added ethyl bromoacetate (13.5 g, 81.3 mmol) and the mixture was heated under reflux for two hours. After partial evaporation of the ethanol the mixture was poured into cold water (100 mL) and the solid which formed was collected. This material was identified as 26 by its NMR spectrum: NMR (CCl$_4$) δ 7.99-7.65 (m, 4, aromatic), 3.92 (q, J = 8 Hz, 2, OCH$_2$), 2.95 (s, 2, CH$_2$C=O), 1.20 (s, 3, CH$_3$), 1.15 (t, J = 8 Hz, 3, CH$_3$).

Ethyl 1,4-dihydroxy-3-methyl-2-naphthoate (27).[42]

Ethyl 2-methyl-1,3-indandione-2-acetate (26) (7.47 g, 30.4 mmol) was added to a solution of sodium (1.75 g, 70.6 mmol) in dry ethanol (300 mL). The reaction mixture was stirred for two hours, cooled, diluted with water (50 mL), then poured into 10% sulfuric acid (500 mL). There were obtained 5.24 g of 27 NMR (CCl$_4$) δ 12.00 (s, 2, OH), 8.30 (m, 1, aromatic), 7.93 (m, 1, aromatic), 7.61-7.28 (m, 2, aromatic), 4.45 (q, J = 8 Hz, 2, OCH$_2$), 2.45 (s, 3, CH$_3$), 1.45 (t, J = 8 Hz, 3, CH$_3$).

Ethyl 1,4-dimethoxy-3-methyl-2-naphthoate (28).

Ethyl 1,4-dihydroxy-3-methyl-2-naphthoate (27) (5.24 g, 21.3 mmol), dimethylsulfate (8.05 g, 64 mmol) and potassium carbonate (5.87 g, 42.5 mmol) were combined in acetone (250 mL) and heated under reflux (nitrogen) for 1 day. After removing the solids by filtration, the solvent was evaporated to give an oil. Excess dimethylsulfate was removed by dissolving the oil in ethyl ether and treating the solution with triethylamine. The cloudy solution that formed was washed successively with water (50 mL), 3N hydrochloric acid (50 mL) and again water (50 mL). The solution was dried over MgSO$_4$ and the ether evaporated to give 28 (5.84 g, 100%) as an orange oil that was decolorized by chromatography (silica gel, 100 g, dichloromethane), NMR (CCl$_4$) δ 8.03 (m, 2, aromatic), 7.45 (m, 2, aromatic), 4.42 (q, J = 8 Hz, 2, OCH$_2$), 3.90 (s, 6, OCH$_3$), 2.38 (s, 3, CH$_3$), 1.45 (t, J = 8 Hz, 3, CH$_3$).

1,4-dimethoxy-3-methyl-2-naphthoic acid (29).

Ethyl 1,4-dimethoxy-3-methyl-2-naphthoate (28), (5.84 g, 21.3 mmol) and potassium hydroxide (7.37 g, 120 mmol), in water (15 mL) and di-methylsulfoxide (50 mL) were heated on the steam bath under nitrogen for 8 hours. The oil which formed when the cool solution was poured into hydrochloric acid (6N 80 mL) was extracted with ether. The ether was dried over $MgSO_4$ and evaporated to give 29 as a semisolid material (3.95 g). NMR (CCl_4) δ 12.26 (br, 1, COOH), 8.10-7.85 (m, 2, aromatic), 7.51-7.25 (m, 2, aromatic), 4.05 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 2.49 (s, 3, CH_3).

1,4-dimethoxy-3-methyl-2-naphthoylnitrile (31).

1,4-dimethoxy-3-methyl-2-naphthoic acid (29) (3.95 g) and thionyl chloride (20 ML) were heated under reflux (nitrogen) for two hours. The thionyl chloride was evaporated to give 4 g of 30 as an oil. IR (neat) 1780 cm^{-1} (C=0 of acyl chloride). Acyl chloride 30 was added to a stirred suspension of cuprous cyanide[40] (2.04 g, 22.8 mmol) in acetonitrile (50 mL) under nitrogen. The mixture was heated under reflux overnight and the solvent was evaporated. Petroleum ether was added to the residue causing a solid material to separate. The solid was filtered off and the solvent was evaporated to give a green oil which after chromatography (silica gel, 100 g, chloroform) furnished pure 31 (1.42 g, 35%), m.p. 93-94°C, NMR (CCl_4) δ 8.19-7.92 (m, 2, aromatic), 7.65-7.35 (m, 2, aromatic), 4.19 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 2.43 (s, 3, CH_3); IR (neat) 2200 (CN), 1680 (C=0) cm^{-1}; u.v. (MeOH) 230, 270 nm.

Ethyl 2-bromomethylbenzoate (32).

Ethyl 2-methylbenzoate (34.5 g, 0.209 mol), N-bromosuccinimide
(44.7 g, 0.251 mol) and benzoyl peroxide (500 mg) were combined in
carbon tetrachloride (600 mL) under nitrogen. The mixture was heated
under reflux for 30 minutes, then irradiated with a sun lamp at reflux
for 6 hours. The mixture was chilled and the succinimide filtered
off. Evaporation of the solvent followed by vacuum distillation of
the liquid residue gave 43 g of 32 (85%), b.p. 95-97°C (0.25 mm);
NMR (CCl$_4$) δ 8.18-7.80 (m, 4, aromatic), 4.90 (s, 2, benzylic), 4.38
(q, J = 8 Hz, 2, OCH$_2$), 1.40 (t, J = 8 Hz, 3, CH$_3$).

Triethyl-1,2,3,4-tetrahydro-4-oxonaphthalene-2,2,3-tricarboxylate (34).

To a stirred suspension of sodium hydride (4.51 g, 94 mmol) in
dry tetrahydrofuran (200 mL) under nitrogen, was added triethyl 1,1,2-
ethane tricarboxylate (23.1 g, 94 mmol). After 20 minutes, ethyl 2-
bromomethylbenzoate (32), (23 g, 94.3 mmol) in tetrahydrofuran (20 mL)
was added rapidly. After stirring for 1 hour, additional sodium
hydride (4.51 g, 94 mmol) and t-butanol (5 mL) were added. The mixture
was refluxed overnight then cooled and treated with acetic acid (40 mL).
The tetrahydrofuran was evaporated at reduced pressure and the residue
taken up in water (150 mL) and extracted with ehtyl acetate (200 mL).
The organic layer was washed with water (3 x 25 mL), dried over
MgSO$_4$, and evaporated to furnish a brown oil. Chromatographic
purification (silica gel, 200 g, benzene) gave 29.7 g (87%) of 34 as

a pale yellow oil. NMR (CCl$_4$) δ 7.99-7.05 (m, 4, aromatic), 4.45-3.95
(m, 8, OCH$_2$ and benzyl), 1.25 (m, 9, CH$_3$), mass spectrum m/e 362 (M$^+$).

1,2,3,4-tetrahydro-4-oxonaphthalene-2-carboxylic acid (35).[20]

Triethyl 1,2,3,4-tetrahydro-4-oxonaphthalene-2,2,3-tricarboxy-
late (34), (29.7 g, 0.82 mol) in glacial acetic acid (250 mL), water
(150 mL), and concentrated hydrochloric acid (100 mL), was heated
on the steam bath for 3 days. Concentration of the solution at re-
duced pressure gave crystals which were collected and washed with
cold water. Dissolution of the crystals in acetone/ethanol and treat-
ment with charcoal gave 35 (11.3 g, 71% yield) as white crystals:
m.p. 145-149°C, (lit.[20] m.p. 145-147°C), NMR (acetone-d$_6$) δ 8.08
(d, J = 8 Hz, 1, aromatic), 7.58-7.19 (m, 3, aromatic), 3.35-2.65
(aliphatic).

Methyl 1,2,3,4-tetrahydro-4-oxonaphthalene-2-carboxylate (36).

A stirred solution of 1,2,3,4-tetrahydro-6-oxonaphthalene-2-
carboxylic acid (35) (7.71 g, 40.6 mol) in ether (100 mL), at 0°C,
was treated with excess ethereal diazomethane. The solution was
stirred for 1 hour at 25°C, then a few drops of acetic acid were added
to destroy the excess diazomethane. There were obtained after
evaporation of the ether 8.27 g, (100%) of 36 as a colorless oil;
NMR (CDCl$_3$) δ 8.05-7.22(m, 4, aromatic), 3.71 (s, 3, OCH$_3$), 3.29-
2.75 (m, 5, aliphatic).

Methyl 1,2,3,4-tetrahydro-4-methylenedioxynaphthalene-2-carboxylate (37).

Methyl 1,2,3,4-tetrahydro-4-oxonaphthalene-2-carboxylate (36),
(5.7 g, 27.9 mmol), ethylene glycol (15 mL), trimethylorthoformate[25]
(25 mL), and p-toluensulfonic acid (10 mg), were combined and heated
at reflux for 10 hours distilling off circa 10 mL of low-boiling liquid.
The mixture at this point showed a faint green phosphorescence. The
solution was cooled, diluted with ether and washed once with sodium
bicarbonate and twice with water. After drying over Na_2SO_4 and
evaporation of the solvent, there was obtained 37 as a thin oil
(5 g, 72%) that crystallized on standing overnight: m.p. 50-53°C,
NMR (CCl_4) δ 7.65-7.09 (m, 4, aromatic), 4.31-4.05 (m, 4, OCH_2), 3.92-
2.85 (m, aliphatic), IR (neat) absence of ketone band at 1690 cm^{-1},
mass spectrum m/e 248 (M^+).

Methyl 1,2,3,4-tetrahydro-4-hydroxynaphthalene-2-carboxylate (38).

To a vigorously stirred solution of methyl 1,2,3,4-tetrahydro-
4-oxonaphthalene-2-carboxylate (36), (8.87 g, 43.5 mmol) in methanol
(250 mL) at 0°C, was added sodium borohydride (1.652 g, 43.5 mmol)
in one portion. The solution was stirred for three hours at which time
TLC analysis (5% EtOAc/$CHCl_3$) indicated that the reaction was complete.
After acidification with 3N hydrochloric acid, the methanol was evapor-
ated and the residue was taken up in ether and washed with water.
The solution was dried ($MgSO_4$) and evaporated to give 38 in quantitative
yield as an oil that acquired a waxy consistency on standing and was

homogeneous by TLC (5% EtOAc/CHCl$_3$), NMR (CCl$_4$) δ 7.41-6.75 (m, 4, aromatic), 4.52 (m, 1, methine), 3.97 (br, 1, OH), 3.58 (s, 3, OCH$_3$), 2.95-1.60 (m, aliphatic).

Methyl 1,2,3,4-tetrahydro-4-t-butyldimethylsiloxynaphthalene-2-carboxylate (39).

To methyl 1,2,3,4-tetrahydro-4-hydroxynaphthalene-2-carboxylate (38), (8.19 g, 39.7 mmol) dissolved in dimethylformamide (20 mL), was added imidazole (6.75 g, 99.3 mmol) followed by t-butyldimethyl-silylchloride (7.19 g, 47.6 mmol). The limpid yellow solution was stirred at 35°C overnight at which time TLC analysis indicated the reaction was complete. Saturated sodium bicarbonate solution was added and the mixture was extracted with ether. The organic layer was washed twice with water, dried over MgSO$_4$ and evaporated to give 12.2 g (95%) of 39 as a pale yellow oil. NMR (CCl$_4$) δ 7.38-6.95 (m, 4, aromatic), 4.82 (m, 1, methine), 3.69 (s, 1, OCH$_3$), 3.10-1.65 (m, aliphatic), 0.98 (s, 9, Si-t-butyl).

1,2,3,4-tetrahydro-4-t-butyldimethylsiloxynaphthalene-2-carbaldehyde (40).

To a stirred solution of methyl 1,2,3,4-tetrahydro-4-t-butyldi-methylsiloxynaphthalene-2-carboxylate (39), (13 g, 40.5 mmol) in dry toluene (400 mL) under nitrogen at -78°C, was added diisobutylaluminum hydride (81 mL, 1M, 81 mmol) dropwise over 1/2 hour. Stirring was continued for two hours at which time the reaction was quenched with isopropanol (100 mL, 2M in toluene). After 30 minutes water (20 mL)

was added and the mixture was allowed to come to room temperature.
Sodium sulfate (50 g) and celite (20 g) were added and after stirring
for 1/2 hour the mixture was filtered. The solvent was dried (MgSO₄),
then evaporated to give 10.7 g (91%) of the pure aldehyde 40 as a
colorless viscous oil: NMR (CCl₄) δ 9.62 (s, 1, CHO), 7.28-7.05 (m,
4, aromatic), 4.82 (m, 1, methine), 3.28-1.85 (m, aliphatic) 0.92 (s,
9, Si-t-butyl).

1,2,3,4-tetrahydro-3-[1-hydroxy-2-(1,3-dithian)-3-pentene]-1-naphthalenol-t-butyldimethylsilyl ether (41).

To a solution of diisopropylamine (0.383 g, 3.79 mmol) in dry
tetrahydrofuran (5 mL) at 0°C under nitrogen, was added n-butyl-
lithium (2.38 mL, 1.6 M, 3.79 mmol). After 10 minutes the solution
was cooled to -78°C and ketene thioacetal 45 (0.552 g, 3.44 mmol)
dissolved in hexamethylphosphoric triamide (3 mL) and tetrahydro-
furan (10 mL) was added dropwise. During 2 hours the solution was
allowed to warm to 25°C (deep red color). After cooling to -25°C,
aldehyde 40 (0.5 g, 1.725 mmol) in tetrahydrofuran (10 mL) was added.
The cooling bath was removed and stirring was continued for two hours.
Saturated ammonium chloride solution was added followed by extraction
with pentane (3 x 30 mL). The organic layer was washed with water
(2 x 20 mL), dried over MgSO₄ and evaporated. Chromatographic purifi-
cation (silica gel, 100 g, CHCl₃) of the residue gave 0.363 g (47%)
of 41 as a pale green oil; TLC analysis (benzene) showed two spots of
very close R.F. values. These two compounds were separated by column
chromatography (silica gel, 100 g, CHCl₃) and were shown to be (NMR)

the two diastereomeric alcohols resulting from attack by 45 on both faces of the aldehyde group. NMR of less polar isomer (CCl4) δ 7.35-6.85 (m, 4, aromatic), 6.05-5.45 (m, 2, vinyl), 4.75 (m, 1, methine), 3.75 (br, s, 1, OH), 2.95 -2.55 (m, 6, CH_2 of dithiane), 1.85 (d, 3, CH_3), 0.98 (s, 9, Si-t-butyl). NMR of more polar isomer (CCl4) δ 7.45-5.90 (m, 4, aromatic), 6.19-5.50 (m, 2, vinyl), 4.88 (m, 1, methine), 3.85 (m, 1, OH), 2.98-2.50 (CH_2 of dithiane), 1.85 (d, 3, CH_3), 0.99 (s, 9, Si-t-butyl). Mass spectrum (both isomers) m/e 450 (M^+).

1,2,3,4-tetrahydro-3-[1-methoxy-2-(1,3-dithian)-3-pentene]-1-naphthalenol-t-butyldimethylsilyl ether (42).

To a stirred suspension of excess sodium hydride in dry tetrahydrofuran (10 mL) under nitrogen at 0°C, were added hydroxy compounds 41 (0.3 g, 0.667 mmol) in tetrahydrofuran (6 mL). After 15 minutes 3 mL of a 1:1 mixture of methyl iodide and hexamethylphosphoric triamide were added dropwise. TLC analysis (CHCl3) showed total disappearance of starting material after 1/2 hour. After stirring for a total of two hours at 0°C the reaction was carefully quenched with a saturated solution of ammonium chloride. The tetrahydrofuran was evaporated and the water layer was extracted with ether which was back-washed with water (3 x 20 mL). The solution was dried (MgSO4) then evaporated. After slug chromatography the methylated compound 42 was obtained in quantitative yield as a pale yellow oil. NMR (of the mixture of isomeric methyl ethers) (CCl4) δ 7.40-6.80 (m, 4, aromatic),

6.10-5.55 (m, 2, vinyl), 4.80 (m, 1, methine), 3.59 (s, 3, OCH$_3$),

3.57 (s, 3, OCH$_3$), 2.75 (m, 6, CH$_2$ of dithiane), 1.85 (d, 6, CH$_3$),

0.98 (s, 18, Si-t-butyl).

1,2,3,4-tetrahydro-3-[1-methoxy-2-(1,3-dithian)-3-pentene]-1-

naphthalenol (43).

Diastereomeric silyl ethers 42 (1 g), were stirred for two days

at 40-45°C in a mixture of acetic acid, tetrahydrofuran and water

(3:1:1). The solvents were removed under vacuum and the residue was

passed through silica gel (5% EtOAc/CHCl$_3$) to give pure hydroxy com-

pounds 43 in quantitative yield as a pale yellow oil. The isomers were

separated by column chromatography (silica gel, 100 g, chloroform).

NMR of less polar isomer (CCl$_4$) δ 8.49-7.85 (m, 4, aryl), 6.10-

6.60 (m, 2, vinyl), 4.65 (m, 1, methine), 3.59 (s, 3, OCH$_3$), 2.85-2.45

(m, 6, CH$_2$ of dithiane), 1.85 (d, J = 6 Hz, 3, CH$_3$). NMR of more polar

isomer (CCl$_4$) δ 8.49-7.85 (m, 4, aryl), 6.10-5.50 (m, 2, vinyl),

4.50 (m, 1, methine), 3.48 (s, 3, OCH$_3$), 2.85-2.45 (m, 6, CH$_2$ of

dithiane), 1.85 (d, J = 6 Hz, 3, CH$_3$).

3-[1-methoxy-2-(1,3-dithian)-3-pentene]-3,4-dihydro-1(2H)-

naphthalenone (44).

To a stirred solution of hydroxy compound 43 in chloroform, was

added excess activated MnO$_2$. After 1 hour, TLC analysis (5% EtOAc/

CHCl$_3$) indicated that the reaction was complete. Filtration through

celite and evaporation of the solvent gave a quantitative yield of

the pure ketone 44. NMR (CCl₄) δ 7.85 (m, 1, aryl), 7.40-7.05 (m, 3, aryl), 6.10-5.50 (m, 2, vinyl), 3.50 (s, 3, OCH₃), 2.98-2.50 (m, 6, CH₂ of dithiane), 1.85 (d, J = 6 Hz, 3, CH₃).

2-propylidene-1,3-dithiane (45).[27]

To a solution of 1,3-dithiane (24 g, 0.20 mol) stirred under nitrogen at -60°C, in dry tetrahydrofuran (200 mL) was added n-butyl lithium (125 mL, 1.59M, 0.20 mol). The solution was allowed to come to 0°C during three hours, then it was cooled to -60°C, at which point trimethylchlorosilane (40 g, 0.37 mol) was added with a syringe. The solution, after warming to room temperature over 4 hours, was cooled to -78°C and n-butyl lithium (125 mL, 1.6 M, 0.2 mol) was added. The solution was allowed to come to 0°C and then was cooled again to -78°C. Propionaldehyde (10.6 g, 0.2 mol) was added and the solution was allowed to reach room temperature overnight. The yellow solution was poured into three times its volume of water and extracted with pentane. The organic layer was washed with water (3 x 30 mL), dried over K₂CO₃ and evaporated. Distillation gave 26 g (81%) of 45, b.p. 65-70°C (0.5 mm), NMR (CCl₄) δ 5.82 (t, J = 8 Hz, 1, vinyl), 2.83 (m, 4, CH₂S), 2.35-2.00 (m, 4, allylic CH₂ and CH₂ beta to sulfur), 1.00 (t, J = 6 Hz, 3, methyl).

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BIOGRAPHICAL NOTE

The author was born in Budapest, Hungary, in 1943. At the age of five, he escaped from Hungary with his parents, brother, and sister. His father, a comptroller in the National Bank of Hungary was in danger of being imprisoned for refusing to join the Communist Party.

The family escaped to Italy where the author attended elementary schools and Lyceo, then worked as a stock broker for the Commercial Bank of Milan. In 1968 he emigrated to the U.S. He worked in various capacities-including laboratory technician and computer programmer-until 1970 when he enrolled in William Jewell College in Liberty, Missouri. During his three years in College, he was named Outstanding Chemistry Student each year. In 1973, he was graduated summa cum laude with a B.A. in chemistry.

In 1974 the author began graduate study in organic chemistry at the Oregon Graduate Center, working with Dr. Frank Hauser on the project which culminated in this thesis.