STRUCTURE AND SYNTHESIS OF LICHEN XANTHONES

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Doctor of Philosophy

of

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by

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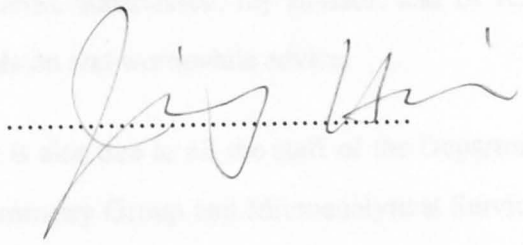
Author's Statement

Except where the work of others is specifically acknowledged,
the research work described in this thesis has been my own.



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Finally, I wish to sincerely thank my wife for her love, support and encouragement.

ABSTRACT

A new synthetic route to lichen xanthones has been developed by using a Smiles rearrangement of an appropriately substituted depside in the key step. Such presursor depsides can be conveniently prepared by the esterification of an appropriately substituted benzoic acid with a substituted phenol in the presence of trifluoroacetic anhydride or dicyclohexylcarbodiimide. Smiles rearrangement of the depside was effected by treatment with anhydrous potassium carbonate and dimethyl sulfoxide at room temperature to afford the isomeric 2-phenoxybenzoic acids. The latter intermediates were subsequently cyclised by treatment with trifluoroacetic anhydride to form the substituted xanthones. This method was found to be particularly valuable in the synthesis of 4-chloronorlichexanthones, 2-dechlorothiomelin and 4-dechlorothiomelin derivatives.

The structure of isoarthothelin (2,5,7-trichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one or 2,5,7-trichloronorlichexanthone) (**1-29**), a metabolite of an Australian *Buellia* species and *Lecanora broccha*, was confirmed by total synthesis using the Friedel-Crafts method.

The new xanthone, 5,7-dichloro-3-*O*-methylnorlichexanthone (**3-25**) has been synthesized and shown to co-occur with 2,5,7-trichloro-3-*O*-methylnorlichexanthone (**3-24**) in the lichen *Lecanora broccha*. The compound (**3-25**) is the first natural norlichexanthone known to exhibit a 5,7-dichloro substitution pattern.

Two further new dichloronorlichexanthone derivatives, 2,5-dichloro-6-*O*-methylnorlichexanthone (**4-8**) and 4,5-dichloro-6-*O*-methylnorlichexanthone (**4-9**),

were shown to be minor constituents of an Australian *Dimelaena* species by chromatographic and spectroscopic comparisons. The identity of these two compounds was established by total synthesis.

The total synthesis of a number of thiomelin derivatives has been completed, including routes to 2,4-dichloro-1-hydroxy-7-methoxy-6,8-dimethyl-9*H*-xanthen-9-one (TH2, **1-38**), 2,4-dichloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthen-9-one (TH3, northiomelin, **5-4**), 4-chloro-1,8-hydroxy-5-methoxy-6-methyl-9*H*-xanthen-9-one (2-dechlorothiomelin, **5-69**), 4-chloro-1-hydroxy-5,8-dimethoxy-6-methyl-9-*H*-xanthen-9-one (2-dechloro-8-*O*-methylthiomelin, **5-3**), 2-chloro-1,8-hydroxy-5-methoxy-6-methyl-9*H*-xanthen-9-one (TH1, 4-dechlorothiomelin, **1-37**), 2-chloro-1-hydroxy-5,8-dimethoxy-6-methyl-9-*H*-xanthen-9-one (4-dechloro-8-*O*-methylthiomelin, **5-2**). Chromatographic (t.l.c. and h.p.l.c.) and spectroscopic (n.m.r. and m.s.) comparisons between the synthetic samples and the natural pigments confirmed the occurrence of these xanthones in the lichen *Rinodina thiomela*.

CONTENTS

Chapter 1. Introduction

1.a. Lichens

A lichen is a special kind of plant being a stable self-supporting association of a mycobiont and a photobiont. The mycobiont (the exhabitant) is the fungal partner in a lichen association, and the photobiont (the inhabitant) is the photosynthetic partner. Photobionts may be either green algae (phycobionts) or cyanobacteria (cyanobionts); cyanobacteria were formerly often referred to as blue-green algae.[66] By light microscopy it can be seen that a lichen is composed of two completely different organisms, green algae or cyanobacteria that are related to free-living algae and colourless fungal threads called hyphae. These two components grow together in a harmonious association referred to as symbiosis. Lichen symbiosis, however, differs basically from all other symbiotic associations in that a new plant body, the thallus, is formed, and this thallus has no resemblance to either the fungus or the alga growing alone. This new composite organism behaves as a single independent plant, the green alga manufacturing carbohydrates by photosynthesis and the fungus metabolising these compounds, shielding the alga from desiccation and making up the bulk of the plant body. Thus both fungus and alga benefit from symbiosis.[61]

A unique feature of the lichen symbiosis is that the thallus is so perfectly developed and balanced that not only is its morphology dissimilar to that of either partner, but its physiology is altered significantly from that of free living fungus and alga. Indeed lichens have the following characteristics:

(i) They are long-lived plants.

(ii) They are found in dry locations (xerophilia) and are resistant to low moisture conditions, in contrast with fungi and algae which require moisture (hydrophilia).

(iii) They are capable of thriving in places of extremely high and low light intensity, whereas algae prefer full light (photophytes) and fungi prefer shade (sciophytes).

(iv) They are comprised of new morphological entities, such as protective devices, supporting structures and reproductive organs.

(v) They are a source of lichen substances which are unique to these symbiotic associations.

The high degree of integration in such symbiotic associations is demonstrated particularly clearly by the appearance of substances and structures that the individual symbionts do not produce.[90]

1.b. Lichen Chemistry

i. Lichen Metabolites

There are two main groups of lichen metabolites: intracellular and extracellular products. The intracellular products are usually the primary metabolites which are essential to life process and bound in the cell walls and the protoplasts. They are often water soluble. Most of the primary (or intracellular) metabolites isolated from lichens are not specific and also occur in free-living fungi and algae, and in higher plants. Examples of the intracellular products include proteins, carbohydrates, free amino acids, vitamins and carotenoids.[16,60,70]

The lichen extracellular products are normally the secondary metabolites. They are deposited on the surface of the hyphae rather than within the cells. These metabolites have no obvious metabolic function, have a restricted taxonomic distribution and are not formed under all circumstances. These products are usually insoluble in water and can only be extracted with organic solvents. The classification of the lichen secondary

metabolites has been based on the specialized pathways along which they are formed.[16,60,70] In general these lichen substances are neutral to slightly acidic phenolic or fatty compounds. They constitute on average 2 to 5 percent of the dry weight of a lichen thallus; in *Parmelia tinctorum* lecanoric acid may constitute up to 36 percent of the dry weight. While a few of the metabolites are orange or yellow pigments, the majority are colourless. They occur in nearly all lichen genera, crustose, foliose, and fruticose and are peculiar to lichens as a group, except for endocrocin, chiodectonic acid, polyporic acid, and thelephoric acid, which have also been found in nonlichenized fungi. The orange or yellow pigments usually occur only in the upper cortex, rarely in the medulla, while most of the colourless substances are deposited in the medulla.[59]

All of the secondary substances for which lichens are famous originate from the fungi.[18,90] In some cases it has been shown that the fungal symbiont alone can be induced to produce lichen substances in culture, including an anthraquinone,[125] four pulvic acid derivatives,[88] a diprotic fatty acid, three chromones,[54] usnic acid, and a depsidone.[83] It is the unique secondary metabolites, which exhibit such structural variation and complexity that have attracted the attention and interest of organic chemists for over a hundred years.[60]

ii. Classification of Lichen Secondary Metabolites

Asahina and co-workers[3] were the first to classify lichen secondary metabolites based on the chemical structures. The more recent classifications of the major secondary products present in lichens are based not on their structures but on their biogenetic origins. The possible biosynthetic pathways to lichen metabolites have been deduced by the following means: analogies to established pathways in nonlichenized fungi,[126,127] a few experimental studies on lichens themselves,[87,89,132,133] observed joint occurrences of compounds, and laboratory interconversions and biomimetic syntheses.[29,38,42] Most

of the secondary products are clearly acetyl-polymalonyl derived, but metabolites derived from the shikimic and mevalonic acid pathways are not uncommon.[18]

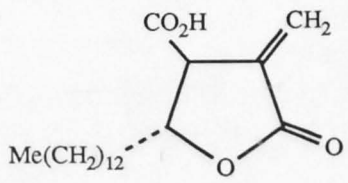
There are three major pathways recognised in this classification, and structural examples of each are given.

I. Acetyl-polymalonyl pathway

A. Aliphatic compounds

1. Higher aliphatic acids, e.g. (+)-protolichesterinic acid **(1-1)**

2. Carbocyclic products, e.g. portentol **(1-2)**



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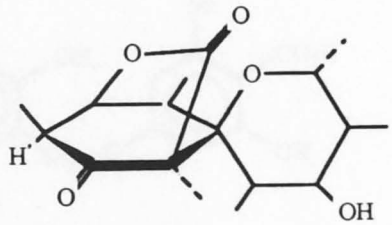

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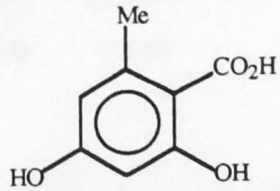
B. Aromatic compounds deriving from a single polyketide chain

1. Mononuclear phenolic compounds, e.g. orsellinic acid **(1-3)**



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2. Multi-aryl derivatives of simple phenolic units. These include

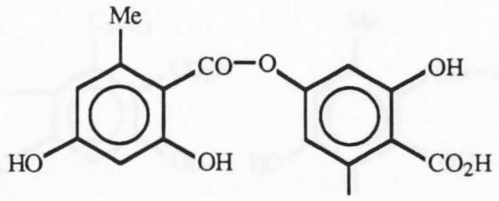
i) depsides, e.g. lecanoric acid **(1-4)**

ii) tridepsides, e.g. gyrophoric acid (**1-5**)

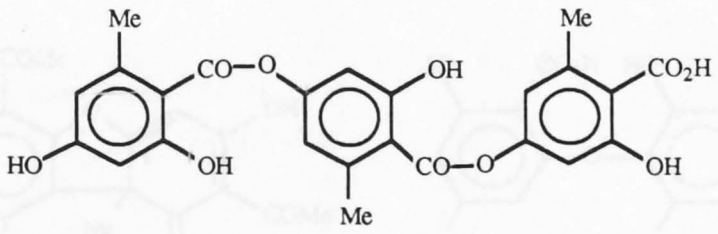
iii) tetradepsides, e.g. aphthosin (**1-6**)

iv) depsidones, e.g. grayanic acid (**1-7**)

v) depsone, e.g. picrolichenic acid (**1-8**)



(**1-4**)



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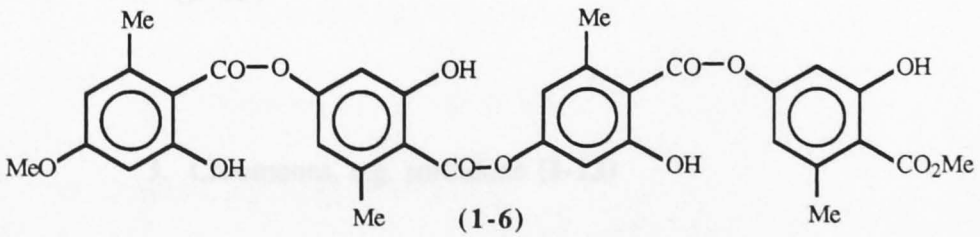

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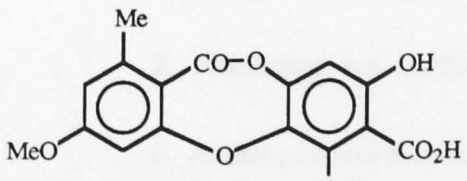

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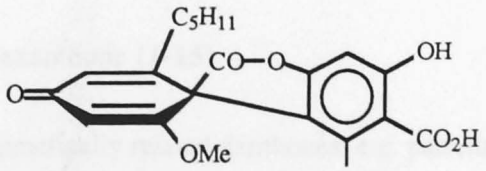


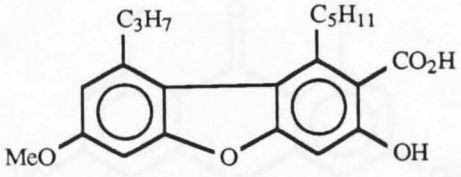
(**1-8**)

vi) dibenzofurans, e.g. didymic acid (**1-9**)

vii) benzyl esters, e.g. barbatolic acid (**1-10**)

viii) phloroglucinol derivatives, e.g. (+)-usnic acid (**1-11**)

ix) diphenyl ethers, e.g. congrayanic acid (**1-12**)



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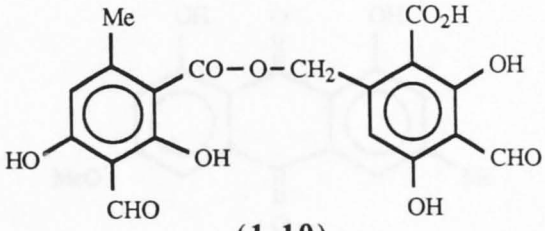

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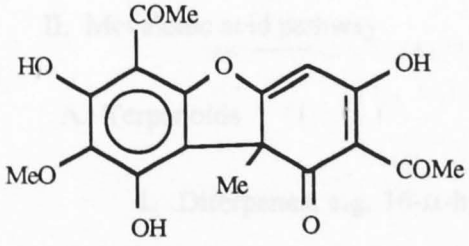

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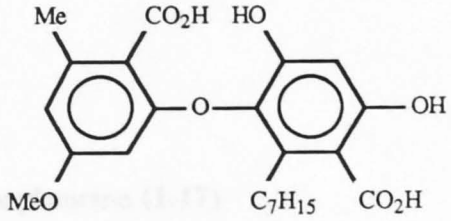

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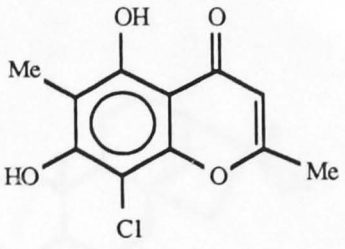
3. Chromones, e.g. sordidone (**1-13**)

4. Naphthoquinones, e.g. haemoventosin (**1-14**)

5. Xanthones, e.g. norlichexanthone (**1-15**)

6. Anthraquinones and biogenetically related xanthones, e.g. parietin (**1-16**)



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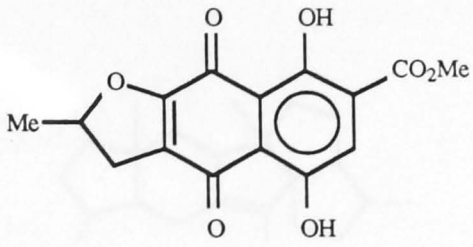

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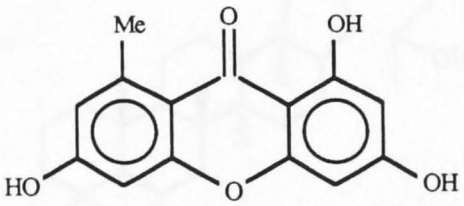

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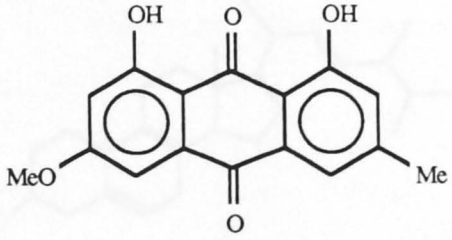

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II. Mevalonic acid pathway

A. Terpenoids

1. Diterpenes, e.g. 16-α-hydroxykaurane **(1-17)**

2. Sesterterpenes, e.g. retigeranic acid a **(1-18)**

3. Triterpenes, e.g. zeorin **(1-19)**

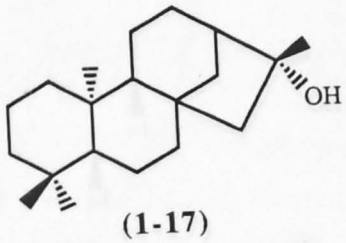
B. Steroids, e.g. lichesterol **(1-20)**

C. Carotenoids, e.g. xanthophyll **(1-21)**

III. Shikimic acid pathway

A. Terphenylquinones, e.g. polyporic acid **(1-22)**

B. Pulvinic acid derivatives, e.g. vulpinic acid **(1-23)**



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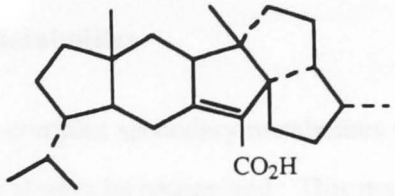

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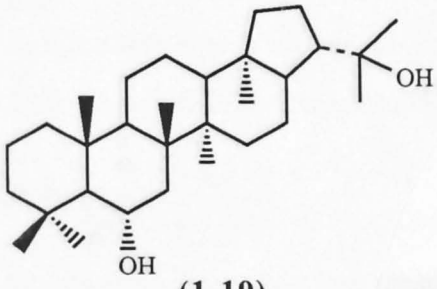

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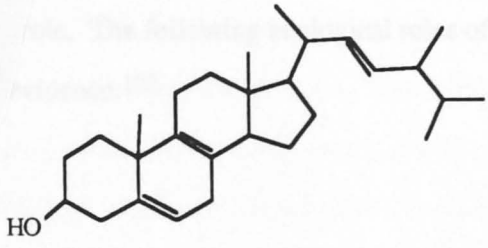

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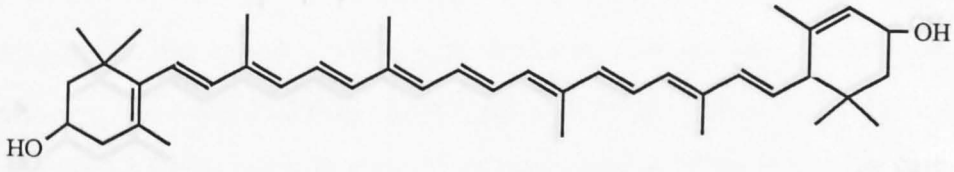

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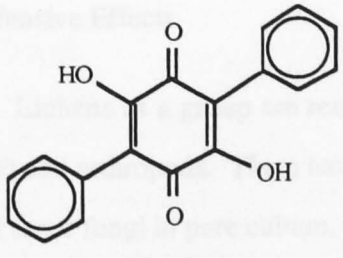

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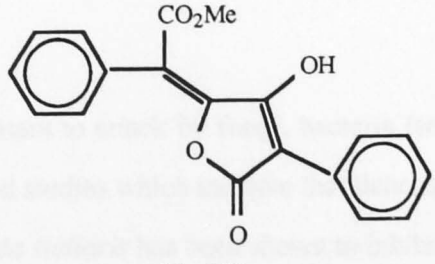

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1.c. The Importance of Lichens

i. The Ecological Role of Secondary Metabolites

In general flowering plants do not form complex secondary metabolites without a specific purpose, although these roles may not always be recognized. This may also be the case with lichens, but here their function has not been critically examined. However the diversity of these compounds and their relatively high concentrations has led to the suggestion that they have a more important role. The following ecological roles of these compounds are supported by experimental evidence.[102]

1. Light Screens

It has been suggested that these metabolites may provide a mechanism for regulating the intensity of light reaching the photosynthetic partner, or the photobiont in the lichen. Pigmented cortical compounds in lichens containing *Trebouxia* have been interpreted as having a role in protecting the photobiont from too much light, since isolates of this alga appear intolerant of excessive illumination. Furthermore, the production of usnic acid **(1-11)** in the field and in isolated mycobionts has been shown to increase with illumination in a variety of macrolichens. This is also the case with parietin **(1-16)** in *Xanthoria parietina* where the thallus colour varies from bright orange-red in exposed sunny sites (due to higher concentrations of this anthraquinone) to greyish yellow in shade.[66]

2. Defensive Effects

Lichens as a group are remarkably resistant to attack by fungi, bacteria (see **ii.** bellow) and arthropods. There have been limited studies which indicate that lichens can inhibit some fungi in pure culture, while *Cladonia stellaris* has been shown to inhibit the growth of *Pinus* seedlings by restricting the growth of mycorrhizal fungi. Grass seedlings may also be inhibited by *Peltigera* species.[66]

Defence against browsing arthropods, gastropods and even mammals may be afforded by lichen products. This is especially so in the case of pulvinic acid derivatives. The lichen *Letharia vulpina* which contains vulpinic acid (**1-23**) has been mixed with powdered glass and used as a poison for wolves in Lapland; hence it was named "wolf's moss". Terpenes may also have a defensive function, since terpene containing lichens tend to be less-grazed than many other subtropical Stictaceae.[66]

3. Biochemical Weathering

Readily soluble lichen acids secreted by the mycobiont have long been implicated as assisting in the biochemical weathering of rocks. It has been suggested that when such lichen compounds interact with suspensions of minerals and rocks, soluble metal-ligand complexes may be formed.[5] This action could assist biochemical weathering of rock and may aid in the attachment of the lichen to substrate.

Chlorinated xanthones, especially frequent in coastal species, could also have a role in enabling lichens to survive in a chloride-rich site.[66]

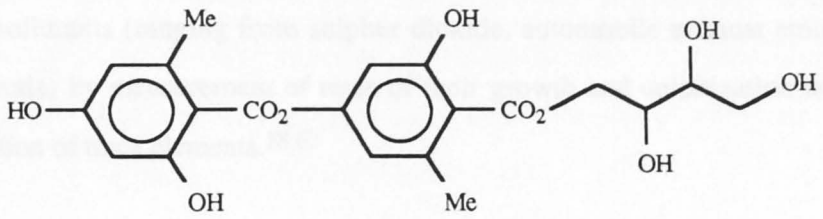
ii. The Uses of Lichens

The use of lichens can be traced back to ancient Egypt and China, where people used lichens in medicines. Nevertheless, today lichens have little direct economic value and their importance is not recognized by the public. The potential commercial uses of lichens are listed below.

1. Medicines

In the 1950s and 1960s, many macrolichens were screened for antibacterial and anti-actinomycete activity, and about half of those studied have been found to be effective against Gram-positive bacteria. The usnic acids (e.g. **1-11**) are especially active and have tumor-inhibiting, antihistamine, spasmolytic and virucidal properties, as well as

being active against Gram-positive bacteria and streptomycetes; they are used in seven commercially available antiseptic creams. Erythrin **(1-24)** from *Roccella montagnei* is



(1-24)

still used in the preparation of erythrityl tetranitrate, a drug sometimes used in the treatment of angina. Compounds with methylene-lactone groups [e.g. protolichesterinic acid **(1-1)**] may also have value as anti-cancer drugs. The medical possibilities of lichen compounds clearly merit further study.[66]

2. Dyeing

Lichens have been used as a source of dyestuffs at least since classical Greek times. Indeed lichen-derived dyes may still occassionally be used in the laboratory. The substances for preparing litmus are derived from lichen *para*-depsides, notably lecanoric acid **(1-4)** (from *Ochrolechia* species), gyrophoric acid **(1-5)** (from *Lasallia pustulata*), and erythrin **(1-24)** (from *Roccella*).[66]

3. Perfumery

Lichen extracts are commercially important in the perfume industry.[76] The extracts are derived from the so-called oak mosses, comprising mainly *Evernia prunastri* and *Pseudevernia furfuracea*, which are collected in large quantities in Yugoslavia, southern France and Morocco. The total annual harvest is estimated at 8000-9300 tons.[91]

4. Pollution Monitors

Lichens have an ability to accumulate minerals from the atmosphere, particularly heavy metals, and are also sensitive to pollutants. Hence lichens have been used to monitor pollutants (ranging from sulphur dioxide, automobile exhaust emissions and heavy metals) by measurement of rates of their growth and colonization and rates of incorporation of trace elements.[18,67]

5. Sources of Food

Man has only used lichens as a source of food in times of emergency. Washington's troops once boiled rock tripes (*Umbilicaria*) in water to extract a gelatinous soup thickener. Lichens have also been used as a fermentation mash in brewing and as a supplementary source of starch in some areas of Europe. In fact, lichens should never be considered seriously as a food as they are often tasteless and many contain bitter, irritating acids.

However lichens are important as animal fodder. Reindeer and caribou in the subarctic conifer forests have long been known to graze in the extensive pastures of reindeer "mosses," *Cladonia alpestris*, *C. rangiferina* and *Cetraria islandica*. Laplanders graze their herds of reindeer on the vast lichen-birch fields of northern Scandinavia and even harvest lichens, much as hay, as a supplementary winter fodder.[59]

6. Sources of Enzymes

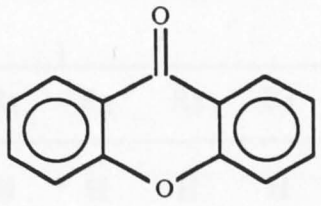
Enzyme systems involved in the production of lichen substances have yet to be widely investigated. However Schultz and Mosbach have isolated a highly specific orsellinate depside hydrolase from *Lasallia pustulata*.[111] This enzyme, apparently a serine esterase of molecular weight *ca.* 42 000, hydrolyses depsides based on orsellinic acid.

7. Lichens in Soil Formation

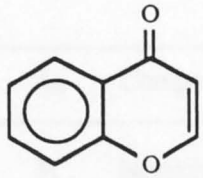
It is believed that lichens take an active part in soil formation, more particularly the breakdown of rocks into soil particles. One hypothesis is that lichen acids can assist in the disintegration of rocks by chelation, a process that removes calcium, magnesium, and other metal ions from the mineral crystals. However their effects in soil formation must be measured in terms of centuries, not decades.[59]

1.d. Lichen Xanthones

The term xanthone (from the Greek meaning yellow) refers to the chemical compound, dibenzo-γ-pyrone **(1-25)**. The xanthones bear a close structural relationship to other naturally occurring γ-pyrone derivatives, such as the chromones **(1-26)**.[110]



(1-25)

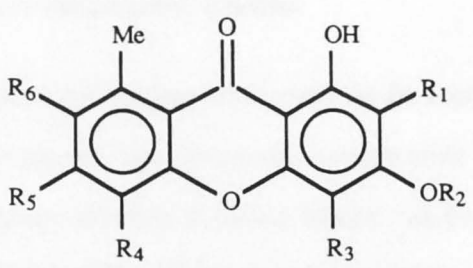


(1-26)

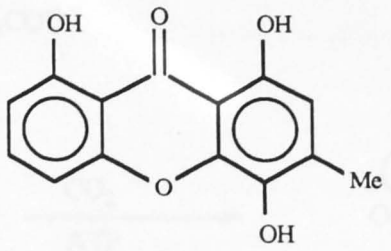
Lichen xanthones are common secondary metabolites occurring outside the cells, often forming yellow crystalline deposits. Xanthone derivatives and structurally related compounds isolated from lichens have been shown to exhibit various and significant pharmacological activity. For example, preliminary evidence indicates that some xanthone glycosides may act on the central nervous system as stimulants or depressants.[117] This has prompted intensive studies of their distribution, biogenesis and properties.

By far the largest proportion of lichen xanthones isolated to date can be regarded as ring chlorinated and / or *O*-methylated derivatives of norlichexanthone (**1-15**). Compounds (**1-27**)-(**1-30**) are typical examples of the norlichexanthone derivatives commonly found in lichens.[19-21,51] One *O*-acetylated lichen xanthone, erythrommone (**1-31**), is also known.[79] In contrast, most fungal xanthones have a substitution pattern similar to that of ravenelin (**1-32**),[63] with little or no nuclear chlorination.

Table 1-1



	R_1	R_2	R_3	R_4	R_5	R_6	Compound
(1-15)	H	H	H	H	H	H	Norlichexanthone
(1-27)	H	Me	H	H	Me	H	Lichexanthone
(1-28)	Cl	H	Cl	Cl	H	H	Arthothelin
(1-29)	Cl	H	H	Cl	H	Cl	Isoarthothelin
(1-30)	Cl	H	Cl	Cl	H	Cl	Thiophanic acid
(1-31)	Cl	Ac	Cl	Cl	Ac	H	Erythrommone



(1-32) Ravenelin

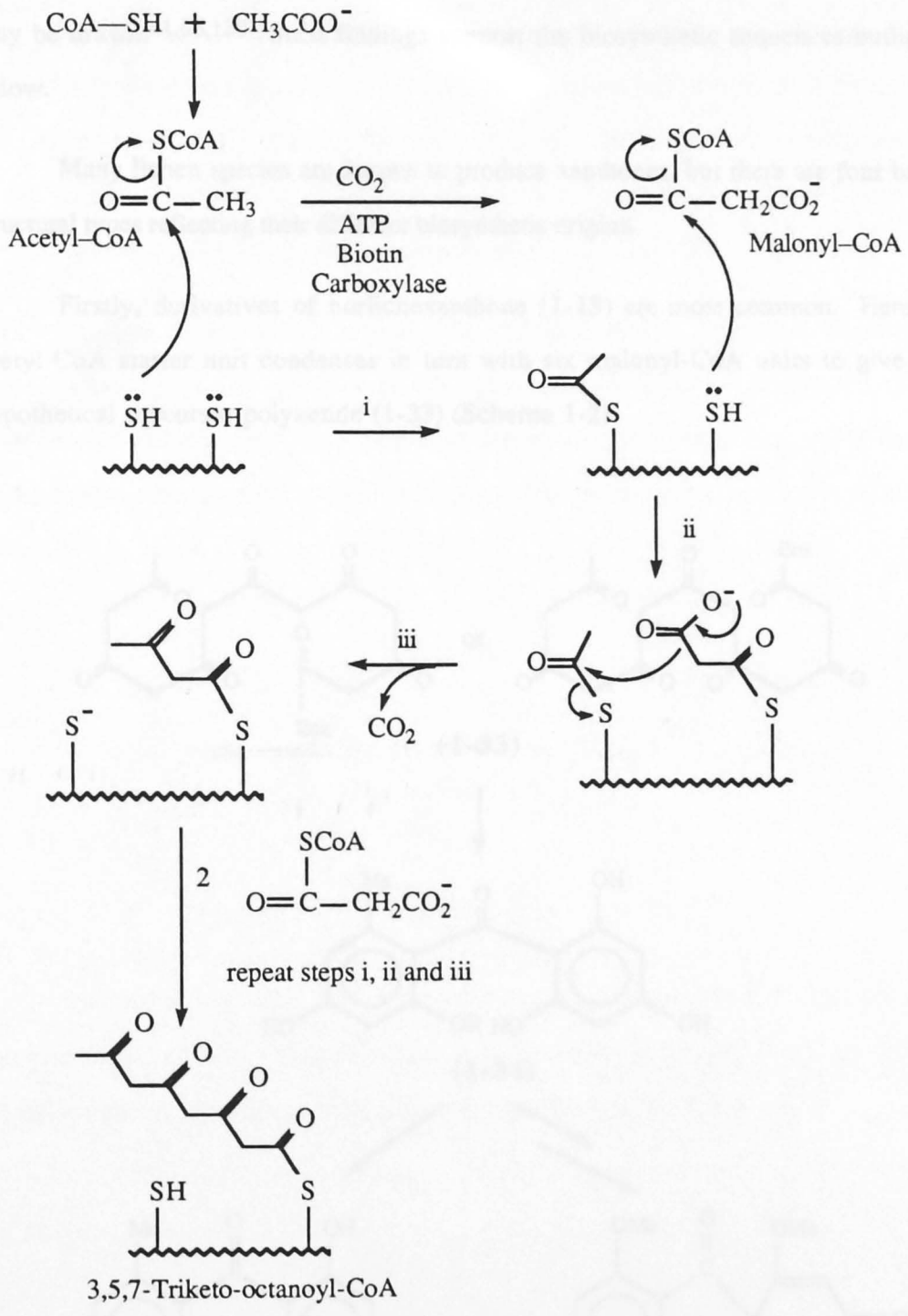
1.e. Biosynthesis of Lichen Xanthones

i. The Biosynthesis of Polyketide Chains

The majority of lichen metabolites are formed via the acetyl-polymalonyl pathway and among these substances the aromatic compounds are most important. Biosynthetically, the primary aromatic building blocks can be considered to originate from a hypothetical polyketide chain. These linear polyketide chains are in turn derived from one molecule of acetyl-coenzyme A (or other acyl-coenzyme A), the "starter" unit, and several molecules of malonyl-coenzyme A (or its homologues).[15,85] The malonyl-CoA is derived, in turn, via carboxylation of acetyl-CoA and is added to the chain by stepwise condensation with concomitant decarboxylation (**Scheme 1-1**).

ii. Formation of Xanthones

When the number of malonyl condensation reactions increases without intermediate reduction steps, longer-chain polyketides (incorporating 7 malonyl units) result and these may ultimately cyclise to form xanthones. This group of compounds cannot be regarded as unique lichen compounds since they also occur in many other organisms, especially the higher fungi and higher plants, although in the latter case the precursor benzophenone is usually partly derived from shikimate rather than solely from malonate.[71]



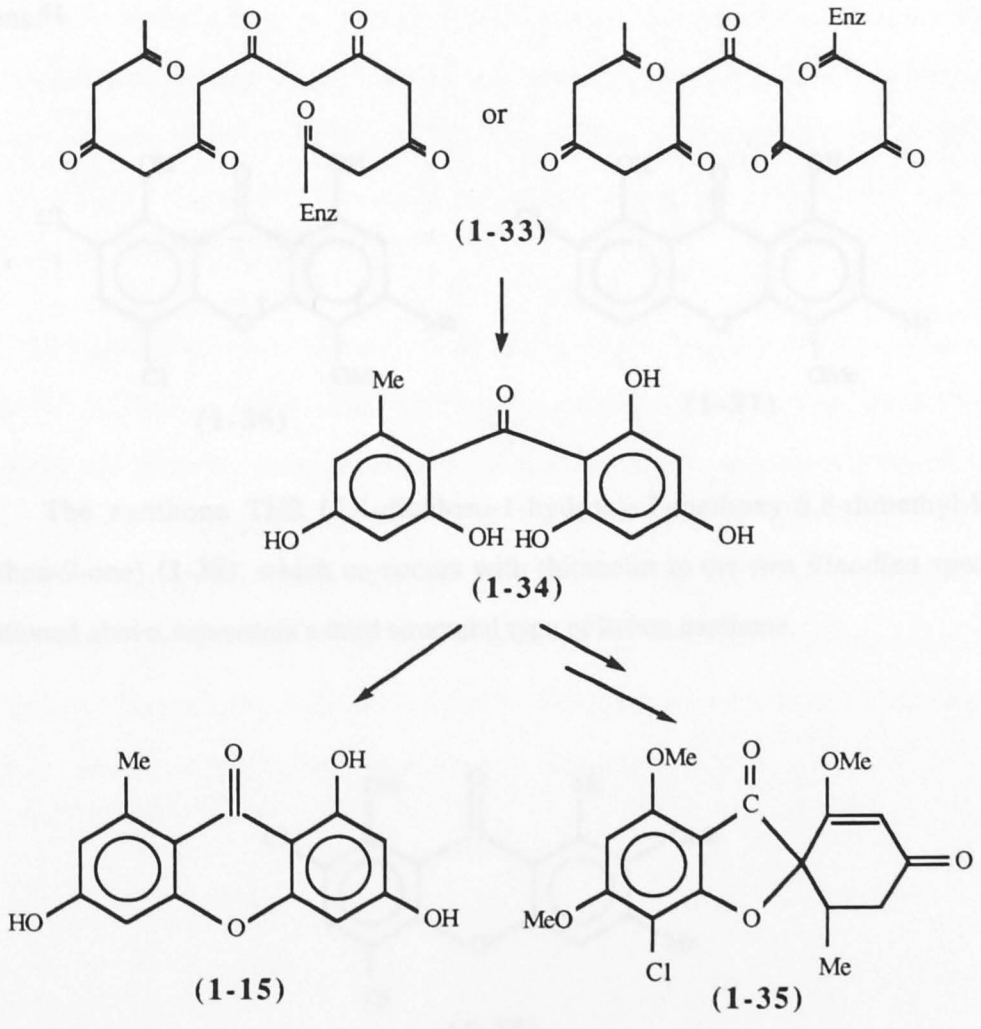
Scheme 1-1

Thus far, no direct studies of the biosynthesis of lichen xanthones have been performed, but parallels with structurally related xanthones found in free-living fungi

may be drawn.[41,63,120] Such findings support the biosynthetic sequences outlined below.

Many lichen species are known to produce xanthones, but there are four basic structural types reflecting their different biosynthetic origins.

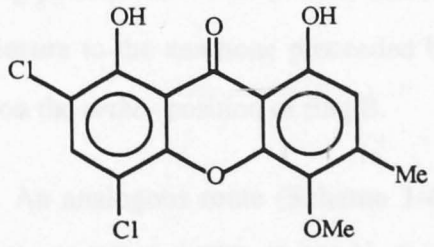
Firstly, derivatives of norlichexanthone (**1-15**) are most common. Here an acetyl-CoA starter unit condenses in turn with six malonyl-CoA units to give the hypothetical precursor polyketide (**1-33**) (**Scheme 1-2**).



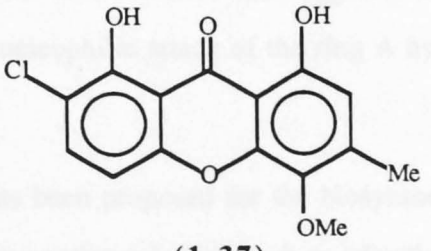
Scheme 1-2

Several studies on the biosynthesis of the fungal metabolite griseofulvin (**1-35**) have demonstrated the dual role of benzophenones as precursors of both griseofulvin and the fungal xanthones.[63] The occurrence of the lichen metabolite norlichexanthone (**1-15**) in fungi has been reported[12,63] and the simplest benzophenone formed from the acetyl-polymalonyl pathway which would yield (**1-15**) is (**1-34**).

Many xanthones isolated from the higher fungi exhibit an alternative substitution pattern as exemplified by ravenelin (**1-32**). Thiomelin (**1-36**) and 4-dechlorothiomelin (**1-37**), isolated from the lichens *Rinodina thiomela* (Nyl.) Müll. Arg. and *R lepida* (Nyl.) Müll. Arg., are two typical examples of ravenelin-type xanthones found in lichens.[41]

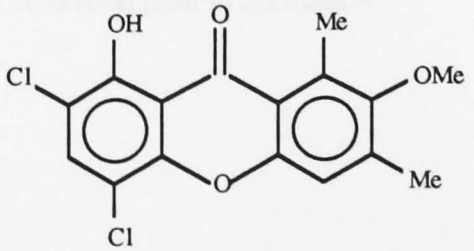


(1-36)



(1-37)

The xanthone TH2 (2,4-dichloro-1-hydroxy-7-methoxy-6,8-dimethyl-9*H*-xanthen-9-one) (**1-38**), which co-occurs with thiomelin in the two *Rinodina* species mentioned above, represents a third structural type of lichen xanthone.

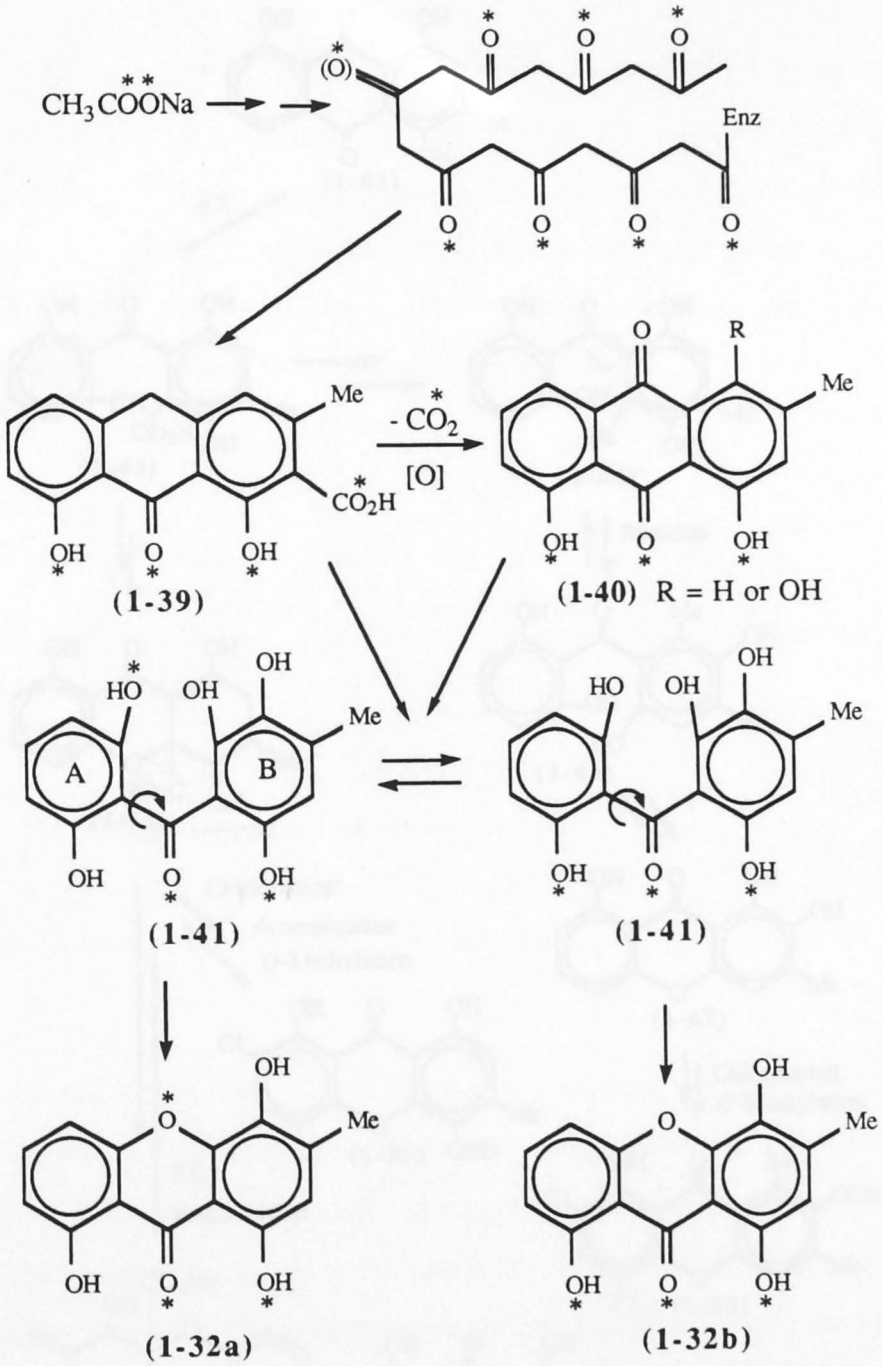


(1-38)

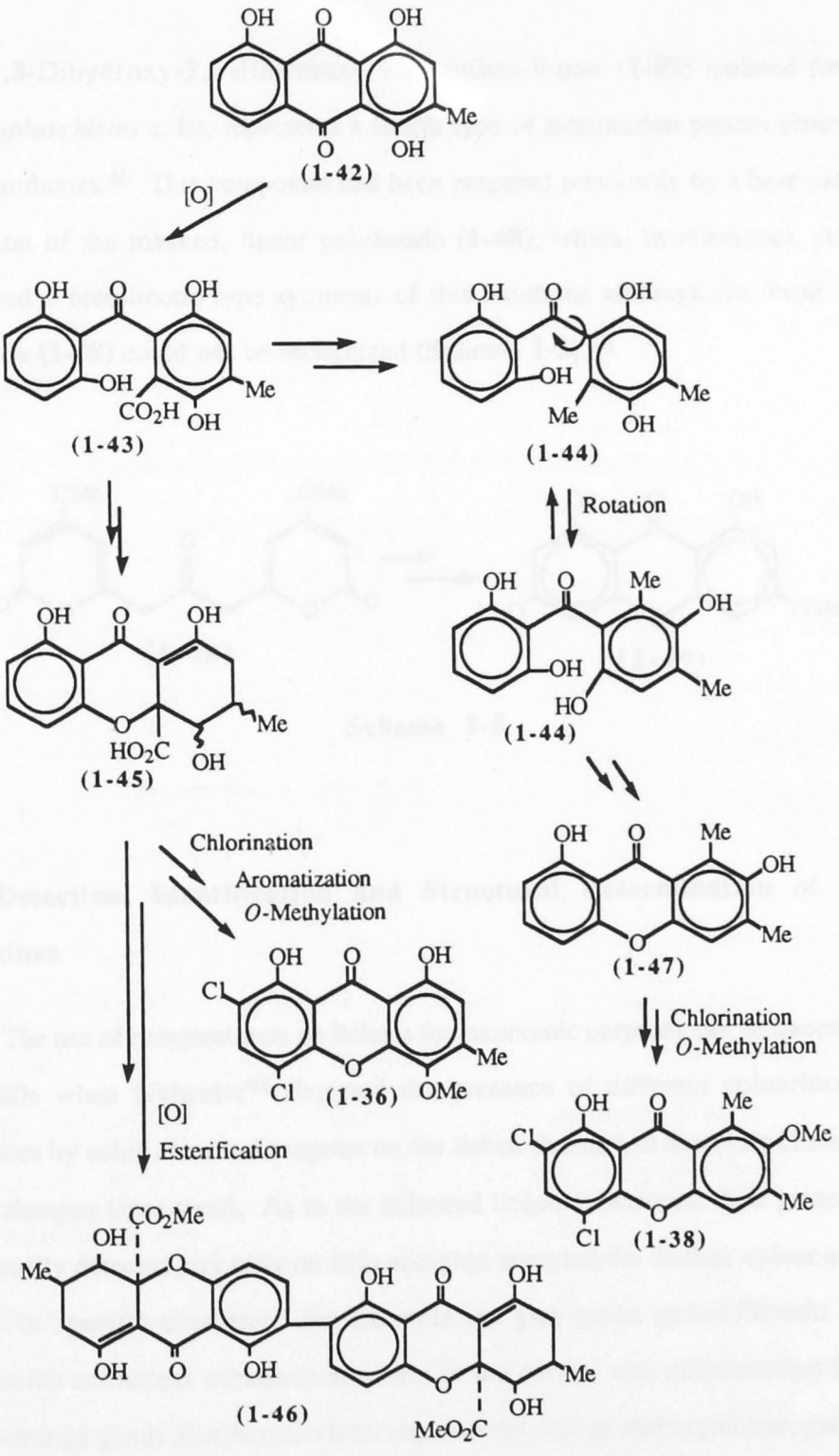
The biosynthesis of these two types of xanthone probably involves the formation of an anthrone or an anthraquinone as an intermediate.[18,41]

Vederas[71] has used incorporation studies of doubly labelled sodium [1-^{13}C, $^{18}O_2$] acetate into ravenelin **(1-32)** with growing cultures of *Drechslera ravenelii* to elucidate the pathway to this fungal xanthone. Using ^{18}O isotopic shifts induced in the ^{13}C n.m.r. spectrum, Vederas proposed the biosynthetic pathway to ravenelin **(1-32)** as outlined in **Scheme 1-3**. In this case cyclisation of a linear polyketide chain gives rise to an intermediate anthrone **(1-39)** or anthraquinone **(1-40)**. Subsequent oxidative cleavage of either **(1-39)** or **(1-40)** gives an intermediate benzophenone **(1-41)**, which cyclises to form the xanthone. This study demonstrated that the symmetrical A-ring of the intermediate benzophenone **(1-41)** may undergo rotation to give two different labelling patterns shown in **(1-32a)** and **(1-32b)**. The evidence also suggested that the ring closure to the xanthone proceeded by nucleophilic attack of the ring A hydroxy group on the *ortho-* position of ring B.

An analogous route (**Scheme 1-4**) has been proposed for the biosynthesis of thiomelin **(1-36)** and TH2 **(1-38)**.[41] Precursor anthraquinones such as islandicin **(1-42)** may undergo an oxidative cleavage to give the intermediate benzophenones **(1-43)** and **(1-44)**. Cyclisation of the benzophenone **(1-43)** would lead to the tetrahydroxanthone **(1-45)**, which could ultimately give the xanthone thiomelin **(1-36)** and the structurally related bis-xanthone, secalonic acid A **(1-46)**, a common lichen metabolite. Alternatively, the intermediate **(1-44)** could give rise to the xanthone TH2 **(1-38)** by rotation of the C-CO bond prior to cyclisation.[41]

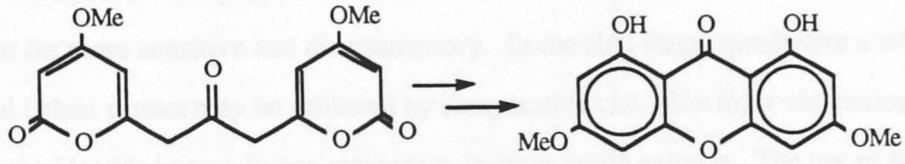

CH3COONa
(O)
Enz
Me
- CO2
[O]
CO2H
R
(1-39)
(1-40) R = H or OH
HO
OH
A
B
(1-41)
(1-41)
(1-32a)
(1-32b)

Scheme 1-3


(1-42)
[O]
(1-43)
(1-44)
Rotation
(1-44)
(1-45)
Chlorination
Aromatization
O-Methylation
(1-36)
(1-47)
Chlorination
O-Methylation
(1-38)
[O]
Esterification
(1-46)

Scheme 1-4

1,8-Dihydroxy-3,6-dimethoxy-9*H*-xanthen-9-one (**1-49**) isolated from the genus *Diploschistes* s. lat. represents a fourth type of substitution pattern observed in lichen xanthones.[40] This compound had been prepared previously by a base-catalysed cyclisation of the masked, linear polyketide (**1-48**), which, in retrospect, could be considered a biomimetic-type synthesis of this xanthone although the 'head' of this polyketide (**1-48**) could not be recognized (**Scheme 1-5**).[18]



(**1-48**) (**1-49**)

Scheme 1-5

1.f. Detection, Identification and Structural Determination of Lichen Xanthones

The use of chemical tests on lichens for taxonomic purposes can be traced back to the 1860s when Nylander[94] detected the presence of different colourless lichen substances by using chemical reagents on the lichen thallus and detecting characteristic colour changes (spot tests). As to the coloured lichen substances, their presence was more readily detected and early on lichenologists accepted the thalline colour as a valid generic or specific character. For example the grey-green genus *Physcia* , which contains the colourless substance atranorin in the cortex, was differentiated from the yellow-orange genus *Xanthoria*, which contains the orange anthraquinone, parietin (**1-16**), in the cortex.

A significant feature common to most of the naturally occurring xanthones is the occurrence of a hydroxy group in the 1 (or equivalent 8) position. Thus they have certain properties in common with 1-hydroxyxanthone itself; for instance, they are yellow in colour, the majority of them give a green colour with ethanolic ferric chloride solution, and they become intensely yellow coloured on contact with 2 *N* sodium hydroxide solution. Some hydroxyxanthones also give positive reactions in colour test with magnesium and hydrochloric acid.[114]

Today, chromatographic methods of detection have superseded spot tests because they are far more sensitive and discriminatory. In the first stage, qualitative analysis of the total lichen extract may be achieved by comparative t.l.c. (thin layer chromatography) in order to identify known lichen substances in these crude extracts. The use of standard solvent systems and materials, combined with the simplicity of performing such t.l.c. analyses and the utility of computer searches, has resulted in this technique being accepted as the "universal" method for characterising known lichen metabolites including the xanthones.[18,46,47]

Another widely used method is h.p.l.c. (high performance liquid chromatography) which, in addition to effecting excellent separation, provides quantitative information about the components present. Individual laboratories with a particular machine and a set of standard solvent systems have used h.p.l.c. to good advantage for characterising known lichen substances by comparison of natural and synthetic compounds.[18]

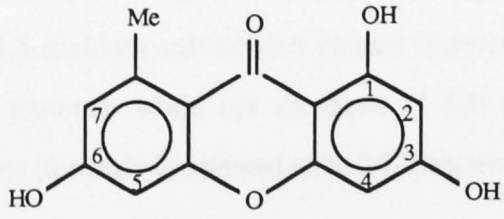
Unlike depsides and depsidones, xanthones are thermally stable since they lack the labile ester linkage. This made it possible for xanthones to be studied by gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS). In 1967, Santesson[103] studied xanthone pigments and obtained mass spectra by introducing small lichen samples into the direct inlet system (lichen mass spectrometry). The xanthones

sublimed as the temperature was raised (100-150°) under very low pressure and although low-mass decomposition products were evident, the xanthones generally gave prominent molecular ions, and the spectra of mixtures could often be seen as a combination of the individual compounds.

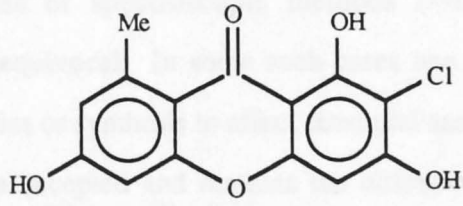
Other advanced instrumental techniques such as ^{1}H n.m.r., ^{13}C n.m.r. and X-ray crystal analysis have proved to be very useful in the identification and structural determination of natural products in general, and lichen xanthones in particular. In fact, the initial structural elucidation can often be made from the spectroscopic data.

In 1942, Asahina and Nogami[2] isolated the first lichen xanthone (lichexanthone) from *Parmelia formosana* Zahlbr. and established the structure **(1-27)** by derivatisation and ultimalely by total synthesis. Since that time a rapidly growing number of xanthones, most of which are chlorinated, have been isolated from lichens. Many are derivatives of the parent compound, norlichexanthone **(1-15)**, but norlichexanthone itself was not found in nature until 1968 when Santesson[104] isolated this substance together with the known arthothelin[78] **(1-28)** from the lichen *Lecanora reuteri*.

Indeed, Santesson was responsible for the isolation of many lichen xanthones[19-21] and structures were deduced with moderate success by chemical degradation, mass spectrometry and ^{1}H n.m.r. spectroscopy. From a comparison of the ^{1}H n.m.r. data for various norlichexanthone derivatives, he found that some of the aromatic protons could be located unambiguously.[106] In general, protons at C2 gave rise to a signal at δ 6.10-6.34 and upon acetylation of either the C1 or C3 hydroxy group, this signal was shifted

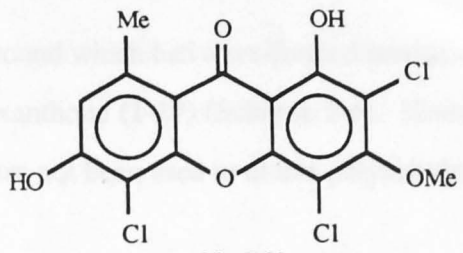


to δ 6.49-6.58. When both these hydroxy groups were acetylated the signal moved further downfield to δ 6.54-6.83. C4 protons resonated in the region δ 6.32-6.61 and as with the C2 protons, were subjected to downfield shifts upon acetylation of the C1 and / or C3 hydroxy groups. Protons at C5 and C7 were usually impossible to distinguish from one another by ^{1}H n.m.r. spectroscopy, both appearing in the δ 6.54-6.79 region, at lower field than the corresponding C2 and C4 protons. These signals were virtually unaffected by acetylation of the "phoroglucinol part" of the xanthone moiety, but a C6 acyl group caused a downfield shift to δ 6.93-7.02. Santesson was successful in utilizing such data in the structural elucidation of some lichen xanthones, e.g. 2-chloronorlichexanthone **(1-50)**.[107]

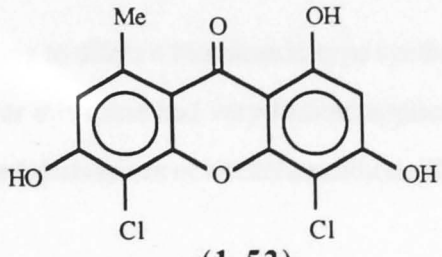


(1-50)

In 1978, Sundholm[118] and Huneck[79] independently published their ^{13}C n.m.r. studies on norlichexanthone derivatives, particularly those chlorinated and / or *O*-methylated derivatives which were not readily distinguished by ^{1}H n.m.r. spectroscopy. They discovered that the large shift difference between carbons C5 (*ca.* δ 100-106) and C7 (*ca.* δ 115-120) were of particular value. Another useful observation was that chloro-substitution caused a downfield shift of *ca.* 3.3-4.4 for the carbon to which the chlorine atom was attached. Subsequent analyses led them to revise the structures of two trichloro-xanthones, arthothelin **(1-28)** and thuringione **(1-51)** and a dichloro-xanthone **(1-52)** obtained from *Lecanora straminea.*[106] Both arthothelin and thuringione were shown to have the 2,4,5-trichloro substitution pattern (formerly assigned the 2,4,7-trichloro substitution pattern); while the xanthone **(1-52)** was shown to be 4,5-dichloronorlichexanthone (formerly considered to be 2,7-dichloronorlichexanthone).



(1-51)



(1-52)

More recently, Elix et al.[41] used X-ray crystal analysis to elucidate the structure of thiomelin **(1-36)**. Such methodology was very effective, but it is expensive and a suitably crystalline derivative must be prepared.

For those lichen xanthones which have a high degree of nuclear chlorination, the application and success of spectroscopic methods (^{13}C and ^{1}H n.m.r., mass spectrometry) is not unequivocal. In some such cases one must revert to the more tedious degradative studies or synthesis to effect structural assignments. Unambiguous synthesis has long been accepted and remains the ultimate tool for confirming the structure of such secondary lichen metabolites, even in the present computer-aided instrumental age.

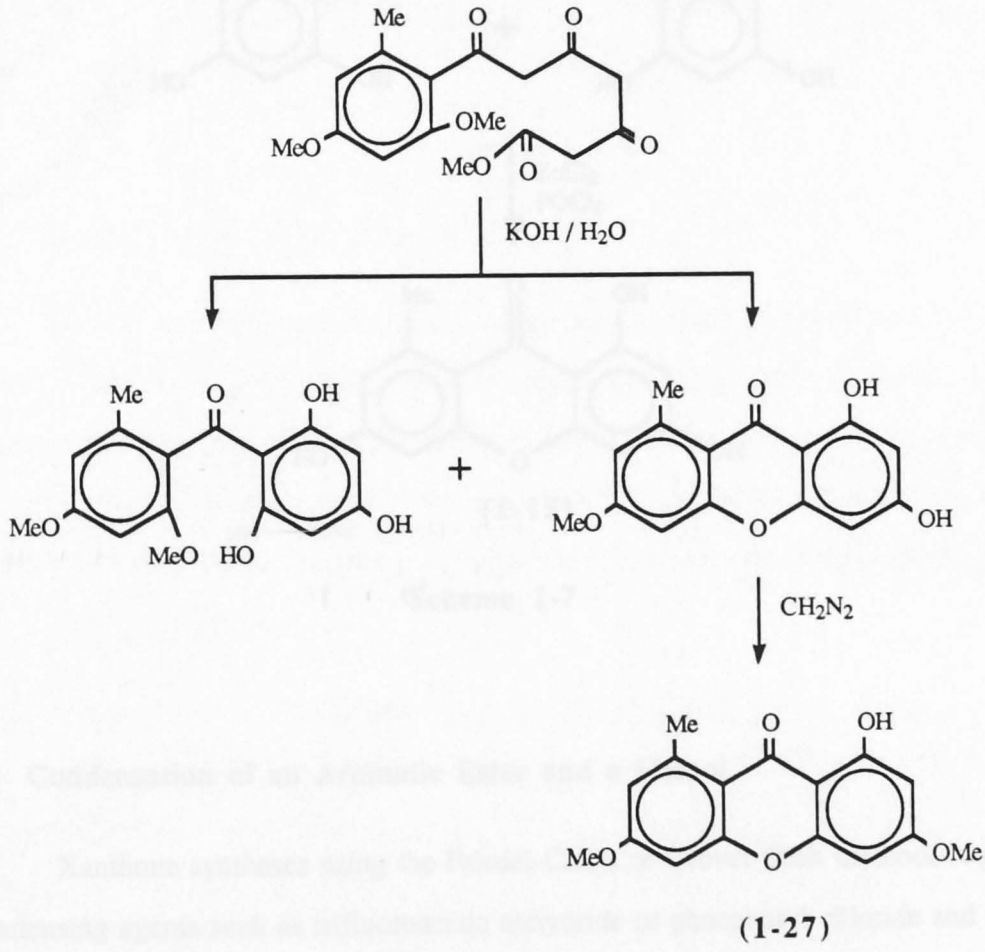
1.g. Chemical Synthesis of Lichen Xanthones

There are number of general methods for synthesizing substituted xanthones and these are reviewed in the following sections. Among them the modified Friedel-Crafts method using trifluoroacetic anhydride (TFAA) is most commonly used today. In the present work a new and convenient route to xanthones via the Smiles rearrangement is described (**Chapter 2**).

i. Biomimetic-type Synthesis

To avoid the problems associated with using a relatively large polyketide chain (that is the numerous cyclisation pathways available) Hay and Harris[64,68] started with a

compound which had a pre-formed aromatic ring to effect a biomimetic-type synthesis of lichexanthone **(1-27)** (**Scheme 1-6**). However this route had very limited applicability and has not been used to obtain polysubstituted derivatives of norlichexanthone (**1-15**).



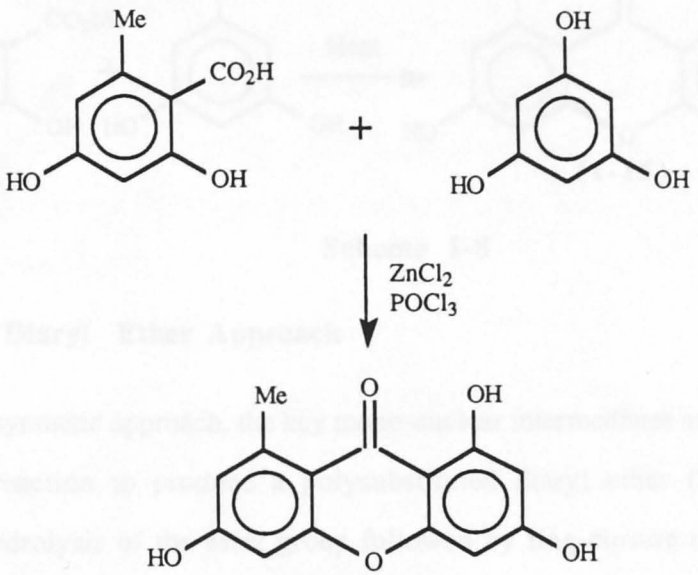
(1-27)

Scheme 1-6

ii. Grover-Shah Synthesis

This method involves the condensation of an appropriately substituted orsellinic acid and phloroglucinol derivatives in the presence of anhydrous zinc chloride and

phosphoryl chloride (**Scheme 1-7**). This direct route works well for norlichexanthone (**1-15**) itself and some simple substituted derivatives, but fails for more highly substituted molecules.[58,113]



(1-15)

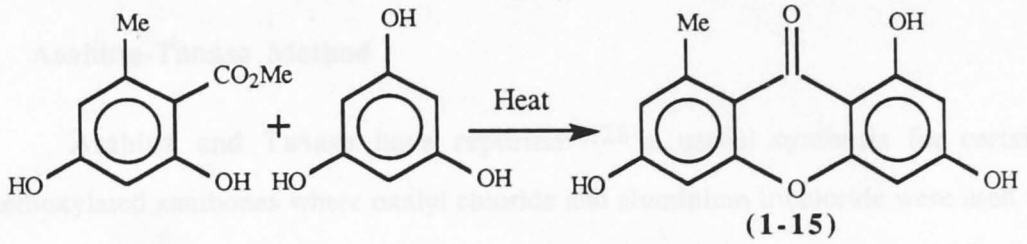
Scheme 1-7

iii. Condensation of an Aromatic Ester and a Phenol

Xanthone syntheses using the Friedel-Crafts or Grover-Shah methods require condensing agents such as trifluoroacetic anhydride or phosphoryl chloride and zinc chloride, which may interfere with sensitive functional groups present. These syntheses also suffer from the disadvantage that the requisite precursor acid derivatives must be obtained from their corresponding methyl or ethyl esters, and this can sometimes result in decarboxylation.

To circumvent these problems Patolia and Trivedi[95] effected the condensation of ethyl or methyl esters of an *ortho*-hydroxyaromatic acid and a phenol by simply heating

the mixture under reflux in diphenyl ether (**Scheme 1-8**). The product xanthones were obtained directly in moderate yield (30-65%).

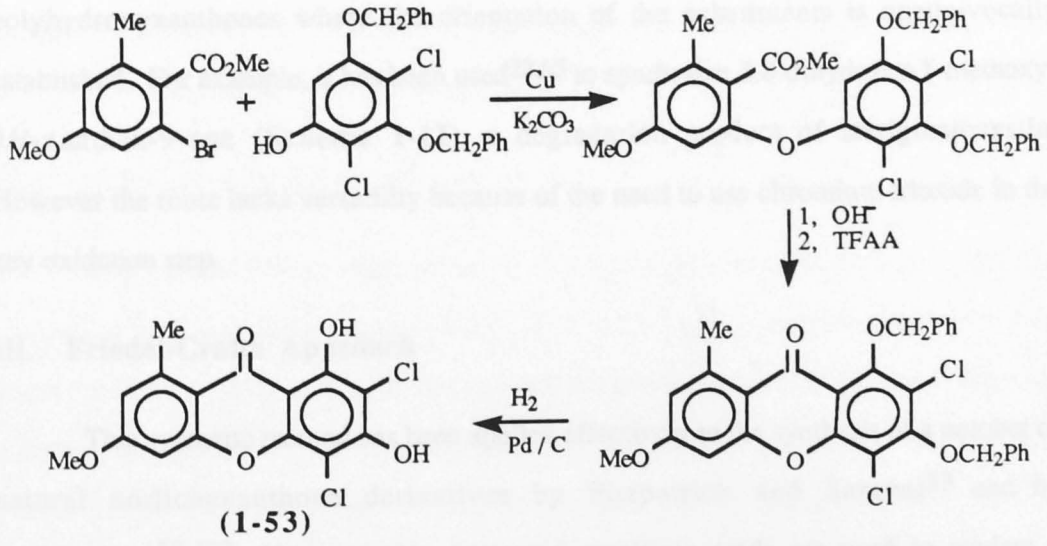


(1-15)

Scheme 1-8

iv. Ullmann Diaryl Ether Approach

In this synthetic approach, the key mono-nuclear intermediates are condensed in an Ullmann reaction to produce a polysubstituted diaryl ether (**Scheme 1-9**). Subsequent hydrolysis of the ester group followed by ring-closure of the resulting carboxylic acid in the presence of trifluoroacetic anhydride (TFAA) or polyphosphoric acid (PPA)[96] afforded the required xanthones. This route was used in the synthesis of



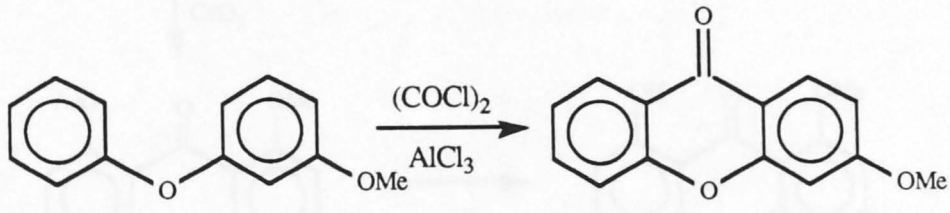
(1-53)

Scheme 1-9

the natural xanthone thiophaninic acid (**1-53**).[49] Although highly selective, this route has a disadvantage in that the key starting bromo-compounds are difficult to prepare.

v. Asahina-Tanase Method

Asahina and Tanase have reported[4,123] a useful synthesis for certain methoxylated xanthones where oxalyl chloride and aluminium trichloride were used to effect the introduction of the C9 carbonyl moiety of a xanthone into a diphenyl ether precursor (**Scheme 1-10**).



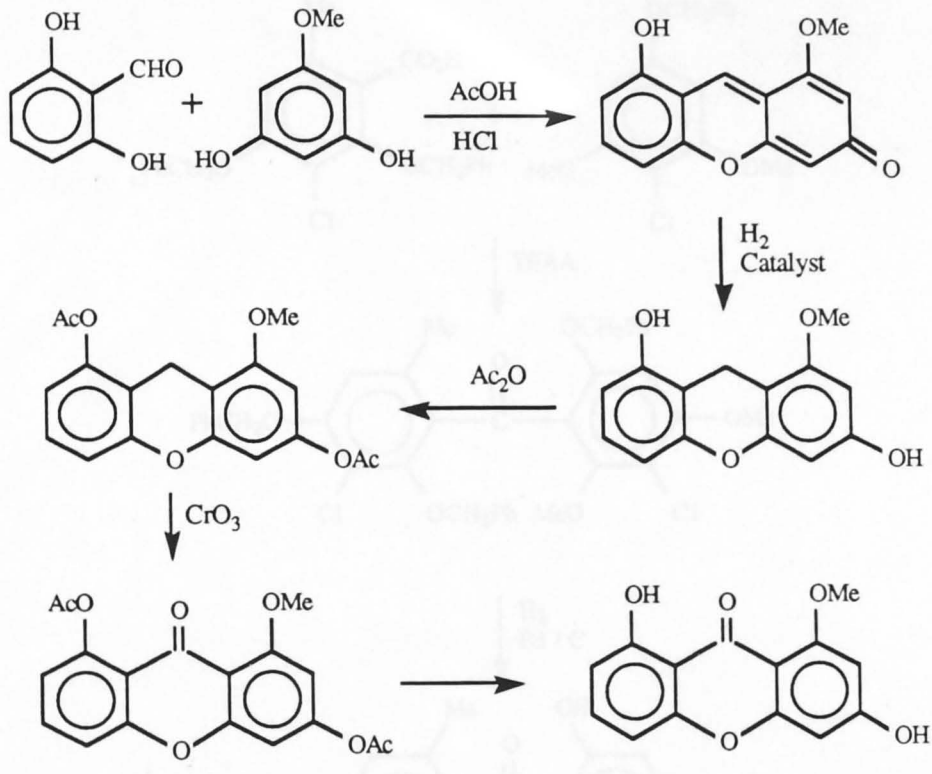
Scheme 1-10

vi. Tanase Method

This elegant method[123] has been used for the preparation of partially methylated polyhydroxyxanthones where the orientation of the substituents is unequivocally established. For example, it has been used[22,65] to synthesize 3,8-dihydroxy-1-methoxy-9*H*-xanthen-9-one (**Scheme 1-11**), a degradation product of sterigmatocystin. However the route lacks versatility because of the need to use chromium trioxide in the key oxidation step.

vii. Friedel-Crafts Approach

This synthetic method has been applied effectively to the synthesis of a number of natural norlichexanthone derivatives by Fitzpatrick and Sargent[53] and by Sundholm.[120,122] Here suitably protected orsellinic acids are used to acylate a phloroglucinol derivative in the presence of trifluoroacetic anhydride to give an intermediate benzophenone. Subsequent deprotection and cyclisation afforded the poly-

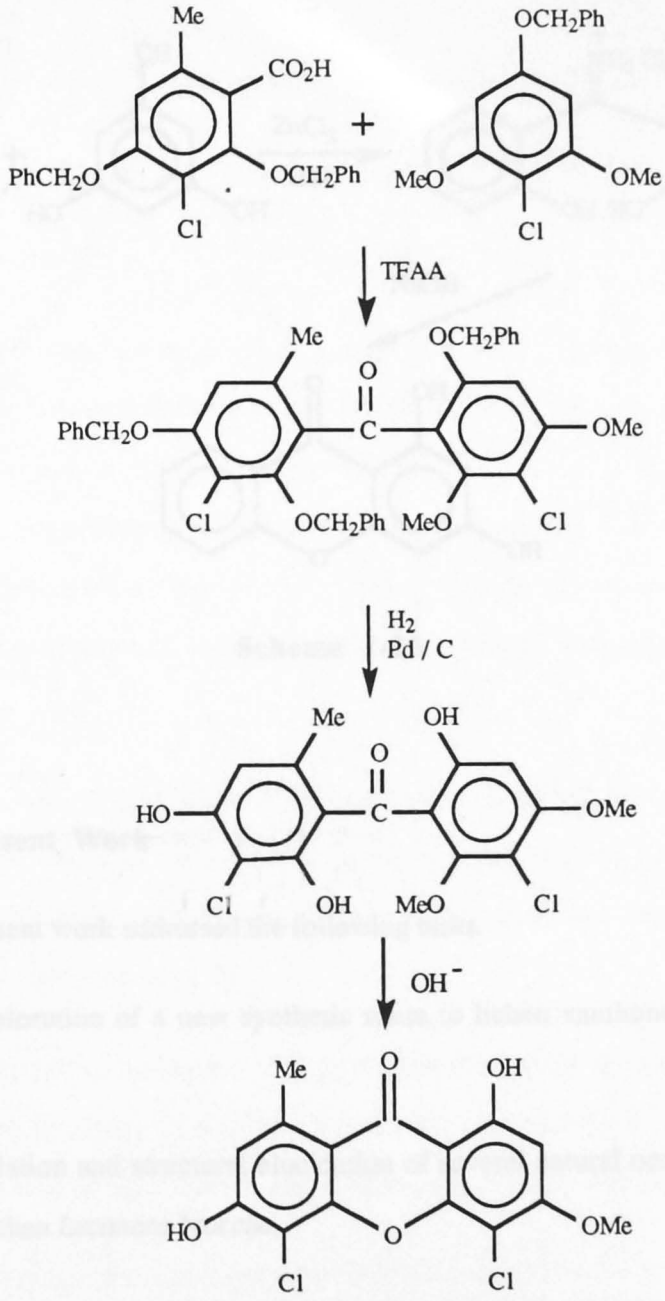


Scheme 1-11

substituted xanthones in reasonable yield (e.g. the synthesis of 4,5-dichloro-3-*O*-methylnorlichexanthone[53] in **Scheme 1-12**).

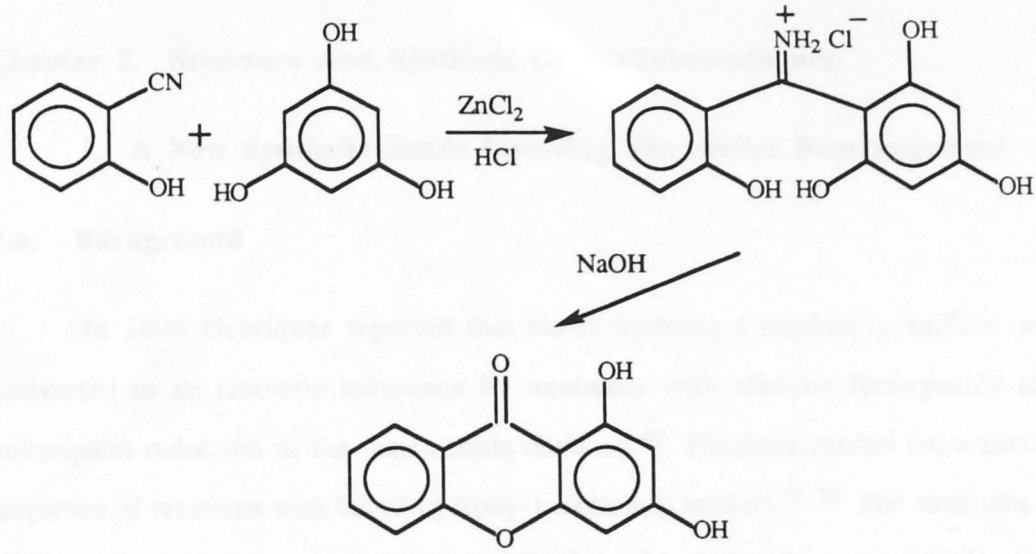
viii. Robinson-Nishikawa Method

This method,[6,93] a variant of the Hoesch synthesis, proceeds through a ketimino compound as illustrated in **Scheme 1-13**. Thus salicylonitrile and phloroglucinol were condensed in the presence of zinc chloride and anhydrous hydrogen chloride to form the corresponding ketimine hydrochloride, which, on boiling with water, gave the free base. The ketimine was readily hydrolysed by aqueous sodium hydroxide to yield 1,3-dihydroxy-9*H*-xanthen-9-one.



(Overall yield : 34%)

Scheme 1-12



Scheme 1-13

1.h. The Present Work

The present work addressed the following tasks.

1) The exploration of a new synthetic route to lichen xanthones via the Smiles rearrangement.

2) The isolation and structural elucidation of several natural occurring xanthones present in the lichen *Lecanora broccha*.

3) The structural elucidation and synthesis of two new xanthones present in an Australian *Dimelaena* species.

4) The total synthesis and structural confirmation of the xanthone TH2 **(1-38)** and various other congenors of thiomelin **(1-36)** present in the lichen *Rinodina thiomela*.

Chapter 2. Structure And Synthesis Of Norlichexanthones

I. A New Synthetic Route Involving The Smiles Rearrangement

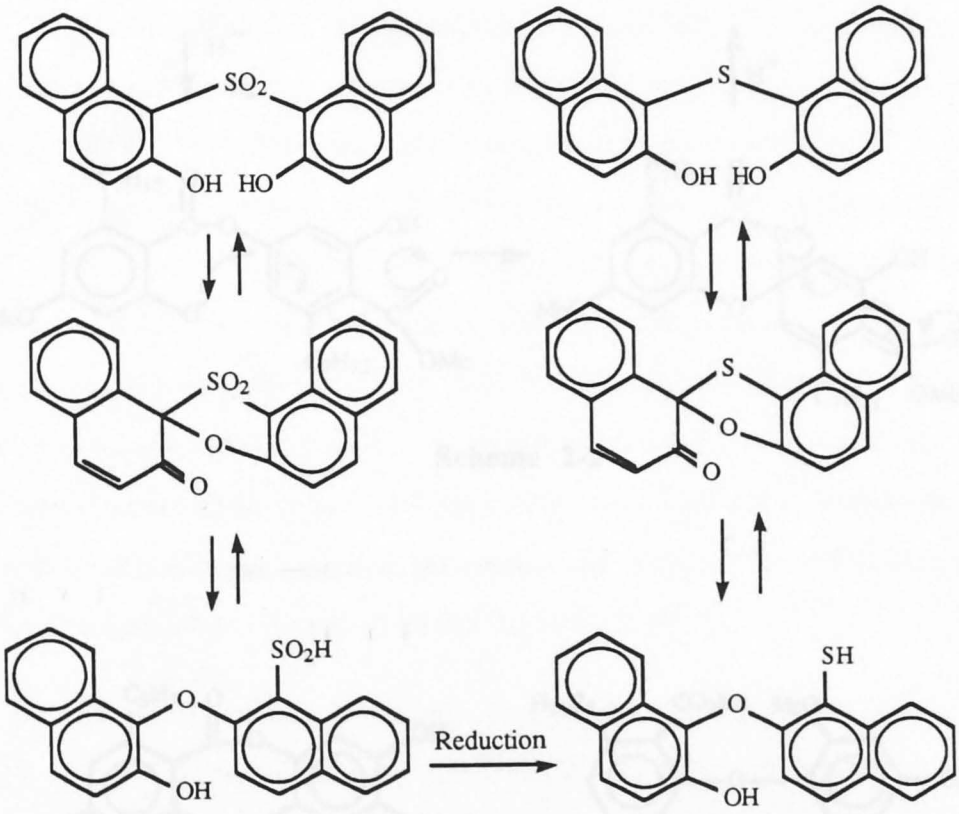
2.a. Background

In 1894 Henriques reported that bis-(2-hydroxy-1-naphthyl) sulfide was converted to an isomeric substance by treatment with alkaline ferricyanide and subsequent reduction of the intermediate obtained.[69] Hinsberg carried out a similar sequence of reactions with bis-(2-hydroxy-1-naphthyl) sulfone.[72-74] The structures of the isomeric products were established by Smiles, who, during the course of this work, recognized the occurrence of a novel intramolecular nucleophilic rearrangement (**Scheme 2-1**).[130,131]

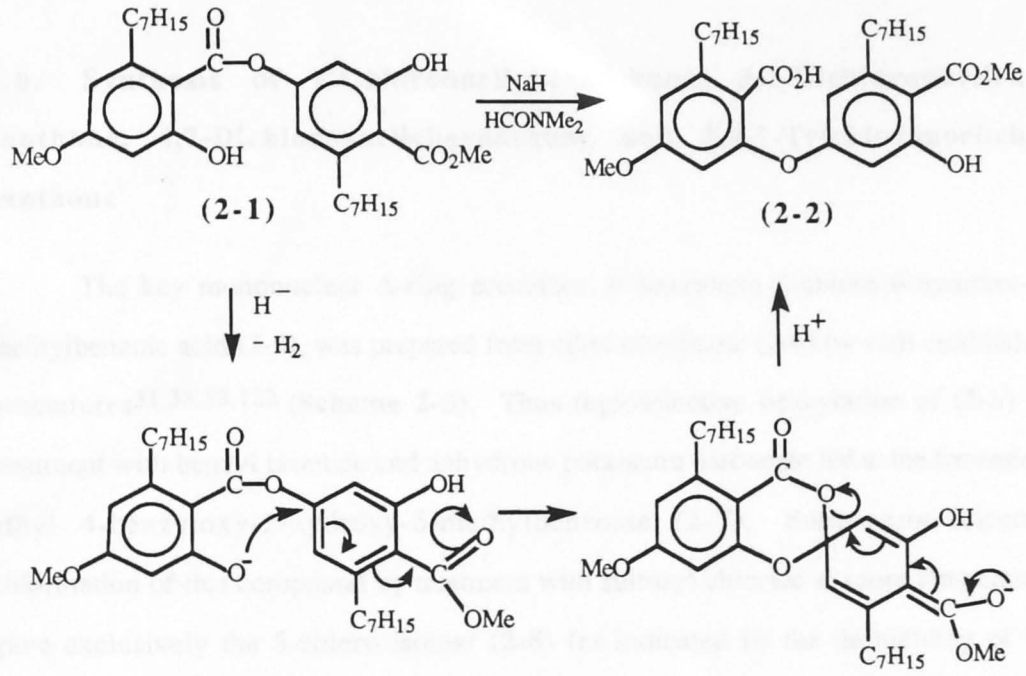
Recently a number of synthetic applications have derived from the key discovery that *para*-depsides such as methyl prasinate (**2-1**) could be readily converted into the isomeric diphenyl ether (**2-2**) through an intramolecular Smiles rearrangement under mild conditions (**Scheme 2-2**).[48]

The Smiles rearrangement of a precursor *meta*-depside was employed in a biomimetic-type synthesis of the depsidones, divaronic acid (**2-3**) and stenosporonic acid (**2-4**),[42] as well as the lichen diphenyl ether, epiphorellic acid (**2-5**).[32]

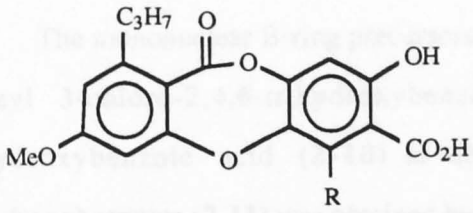
This rearrangement appeared to provide a convenient route to highly substituted 2-phenoxybenzoic acids, already known as appropriate intermediates in the synthesis of 8-methylxanthen-9-ones.[49,53] Hence the viability and synthetic potential of the Smiles rearrangement of appropriately substituted *para*-depsides was investigated as a key step in the synthesis of natural lichen xanthones. In addition, several alternative synthetic methods to particularly substituted xanthones were explored.



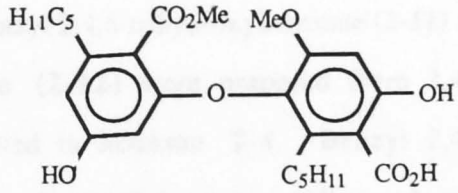
Scheme 2-1



Scheme 2-2



(2-3), R= C_3H_7
(2-4), R= C_5H_{11}



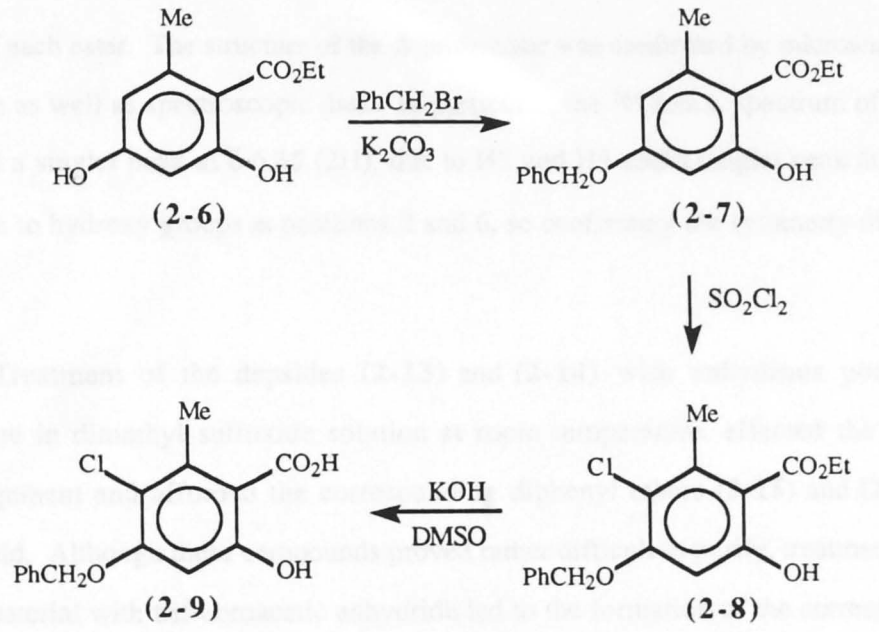
(2-5)

2.b. Synthesis of 7-Chlorononorlichexanthone, 2,7-Dichlorononorlichexanthone, 4,7-Dichlorononorlichexanthone and 2,4,7-Trichlorononorlichexanthone

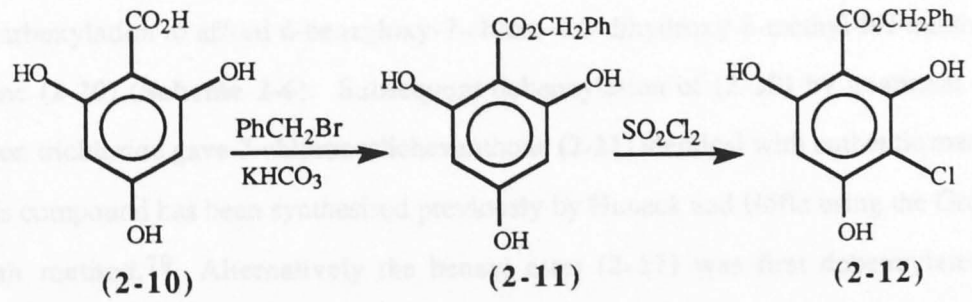
The key mononuclear A-ring precursor, 4-benzyloxy-3-chloro-6-hydroxy-2-methylbenzoic acid (**2-9**), was prepared from ethyl orsellinate (**2-6**) by well established procedures[31,33,53,122] (**Scheme 2-3**). Thus regioselective benzylation of (**2-6**) by treatment with benzyl bromide and anhydrous potassium carbonate led to the formation of ethyl 4-benzyloxy-2-hydroxy-6-methylbenzoate (**2-7**). Subsequent selective chlorination of this compound by treatment with sulfuryl chloride at room temperature gave exclusively the 5-chloro isomer (**2-8**) (as indicated by the deshielding of the adjacent *C*-methyl signal in the ^{1}H n.m.r. spectrum of (**2-8**)). Other orsellinate esters have been shown to undergo similar selective chlorination reactions with this reagent.[105] Ultimate hydrolysis of the ester (**2-8**) by reaction with potassium hydroxide in aqueous dimethyl sulfoxide led to the required benzoic acid (**2-9**).

The mononuclear B-ring precursors benzyl 2,4,6-trihydroxybenzoate (**2-11**) and benzyl 3-chloro-2,4,6-trihydroxybenzoate (**2-12**) were prepared from 2,4,6-trihydroxybenzoic acid (**2-10**) as depicted in **Scheme 2-4**. Benzyl 2,4,6-trihydroxybenzoate (**2-11**) was obtained by benzylation of the corresponding carboxylic acid (**2-10**) with benzyl bromide and potassium hydrogen carbonate in *N,N*-dimethylacetamide solution. Treatment of the benzyl ester (**2-11**) with one mole of sulfuryl chloride under mild conditions then afforded the corresponding mono-chloro derivative, benzyl 3-chloro-2,4,6-trihydroxybenzoate (**2-12**).

The condensation of 4-benzyloxy-3-chloro-6-hydroxy-2-methylbenzoic acid (**2-9**) with benzyl 2,4,6-trihydroxybenzoate (**2-11**) and benzyl 3-chloro-2,4,6-trihydroxybenzoate (**2-12**) in the presence of trifluoroacetic anhydride (**Scheme 2-5**)



Scheme 2-3



Scheme 2-4

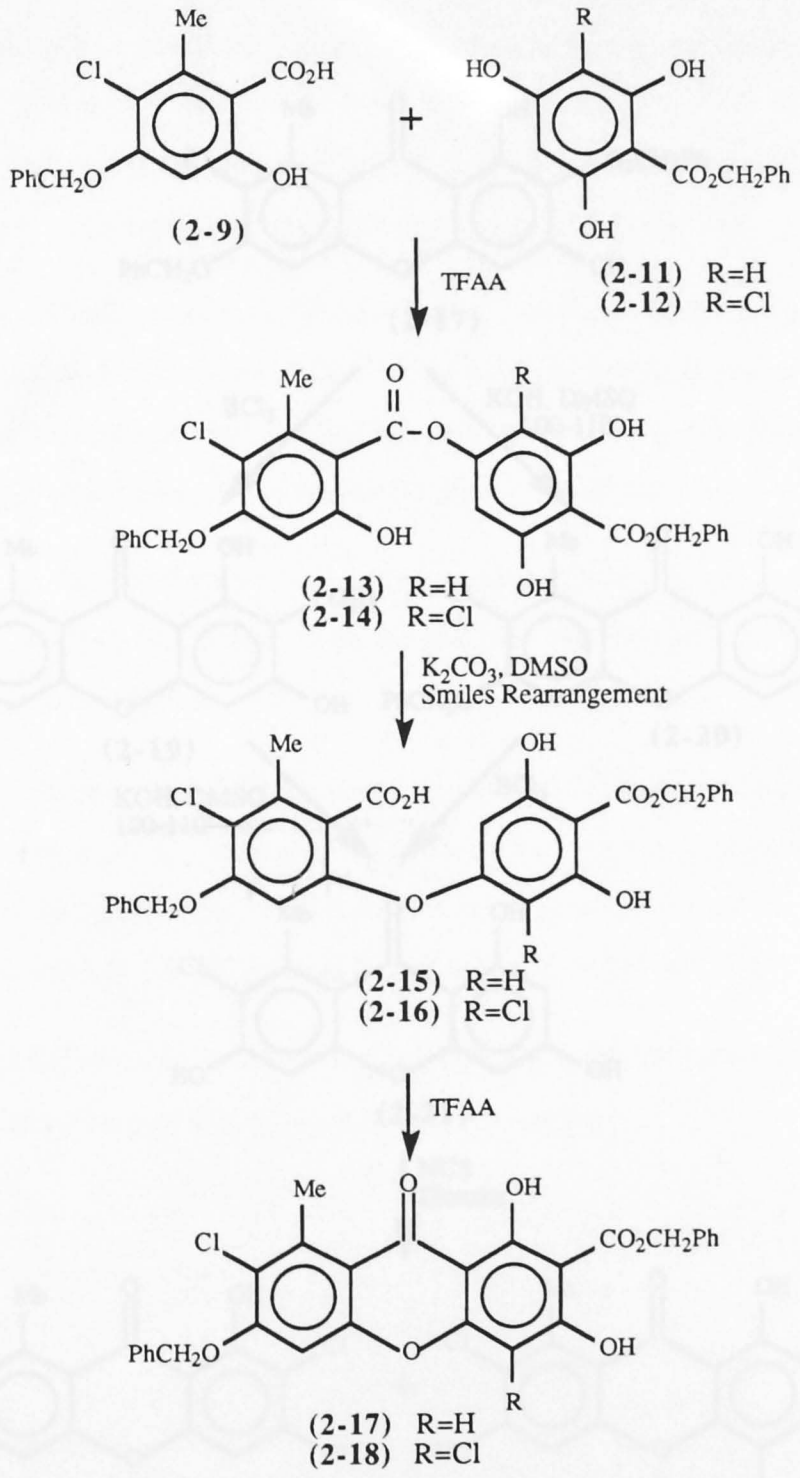
afforded the corresponding depside esters **(2-13)** and **(2-14)** respectively in reasonable yield. Regioselective esterification of the phenolic esters **(2-11)** and **(2-12)** occurred at the less hindered, non or weakly intramolecularly hydrogen bonded phenolic hydroxy

group of each ester. The structure of the depside ester was confirmed by microanalytical evidence as well as spectroscopic data. In particular, the ^{1}H n.m.r. spectrum of (**2-13**) revealed a singlet peak at δ 6.35 (2H), due to H3 and H5 and a singlet peak at δ 9.90 (2H) due to hydroxy groups at positions 2 and 6, so confirming the symmetry of the B-ring.

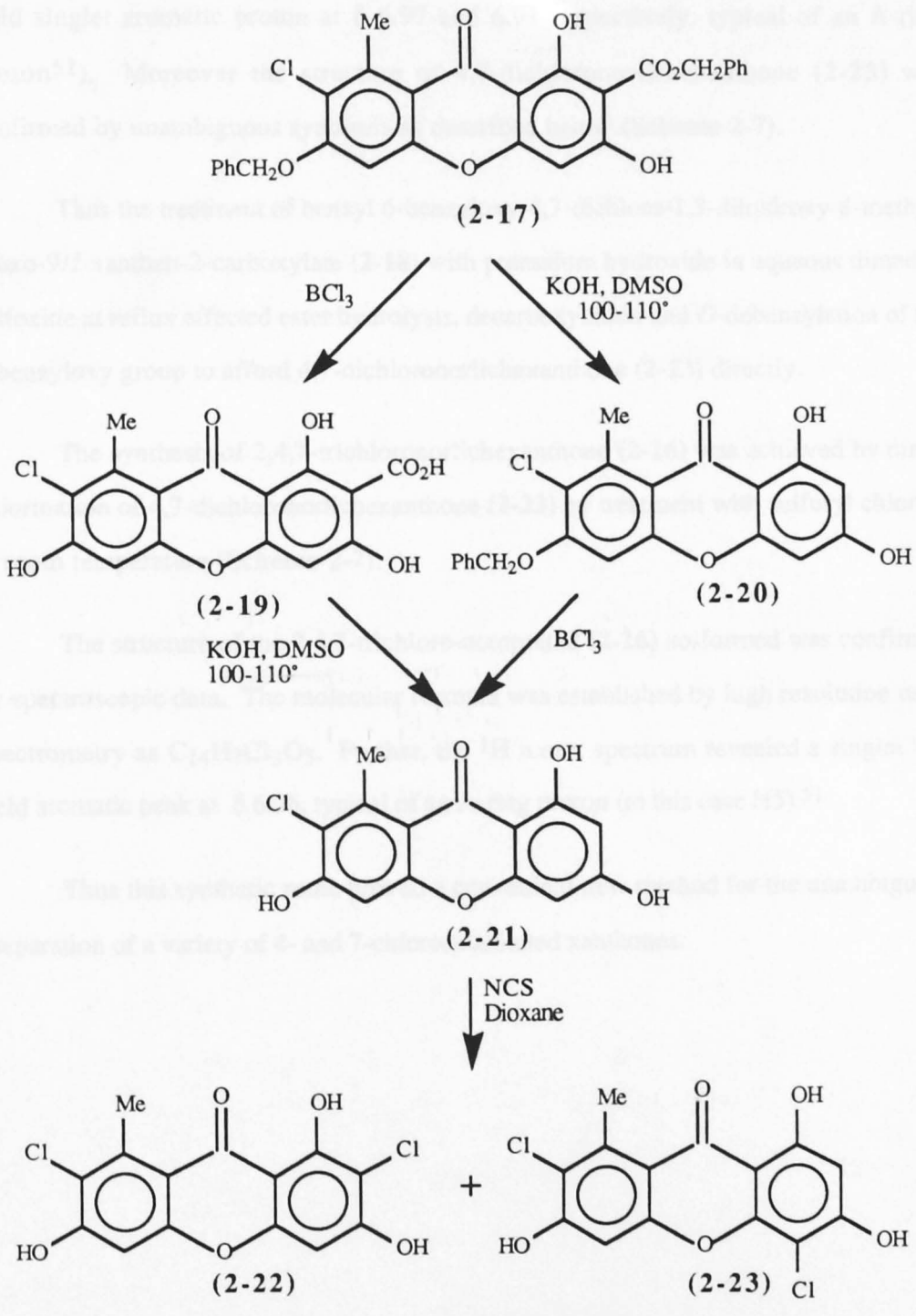
Treatment of the depsides (**2-13**) and (**2-14**) with anhydrous potassium carbonate in dimethyl sulfoxide solution at room temperature, effected the Smiles rearrangement and afforded the corresponding diphenyl ethers (**2-15**) and (**2-16**) in high yield. Although these compounds proved rather difficult to purify, treatment of the crude material with trifluoroacetic anhydride led to the formation of the corresponding xanthones, benzyl 6-benzyloxy-7-chloro-1,3-dihydroxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylate (**2-17**) and the 4,7-dichloro derivative (**2-18**) respectively (**Scheme 2-5**).

The treatment of the benzyl ester (**2-17**) with potassium hydroxide in aqueous dimethyl sulfoxide solution at 100-110° for 5 h effected hydrolysis and concomitant decarboxylation to afford 6-benzyloxy-7-chloro-1,3-dihydroxy-8-methyl-9*H*-xanthene-9-one (**2-20**) (**Scheme 2-6**). Subsequent debenzylation of (**2-20**) by treatment with boron trichloride gave 7-chloronorlichexanthone (**2-21**) identical with authentic material. This compound has been synthesised previously by Huneck and Höfle using the Grover-Shah method.[79] Alternatively the benzyl ester (**2-17**) was first debenzylated by treatment with boron trichloride and the carboxylic acid (**2-19**) so produced, subsequently decarboxylated by treatment with hot potassium hydroxide to afford (**2-21**).

The chlorination of 7-chloronorlichexanthone (**2-21**) was also investigated. With *N*-chlorosuccinimide and a catalytic amount of toluene-4-sulfonic acid in boiling dioxan, the major product was the 4,7-dichloro compound (**2-23**) while the minor product was 2,7-dichloronorlichexanthone (**2-22**). The respective ^{1}H n. m.r. spectra


Me
Cl
CO2H
PhCH2O
OH
(2-9)
+
R
HO
OH
CO2CH2Ph
OH
(2-11) R=H
(2-12) R=Cl
TFAA
O
C–O
(2-13) R=H
(2-14) R=Cl
K2CO3, DMSO
Smiles Rearrangement
(2-15) R=H
(2-16) R=Cl
TFAA
(2-17) R=H
(2-18) R=Cl

Scheme 2-5


Me
O
OH
Cl
CO2CH2Ph
PhCH2O
O
OH
(2-17)
BCl3
KOH, DMSO
100-110°
Me
O
OH
Cl
CO2H
HO
O
OH
(2-19)
Me
O
OH
Cl
PhCH2O
O
OH
(2-20)
KOH, DMSO
100-110°
BCl3
Me
O
OH
Cl
HO
O
OH
(2-21)
NCS
Dioxane
Me
O
OH
Cl
Cl
HO
O
OH
(2-22)
+
Me
O
OH
Cl
HO
O
OH
Cl
(2-23)

Scheme 2-6

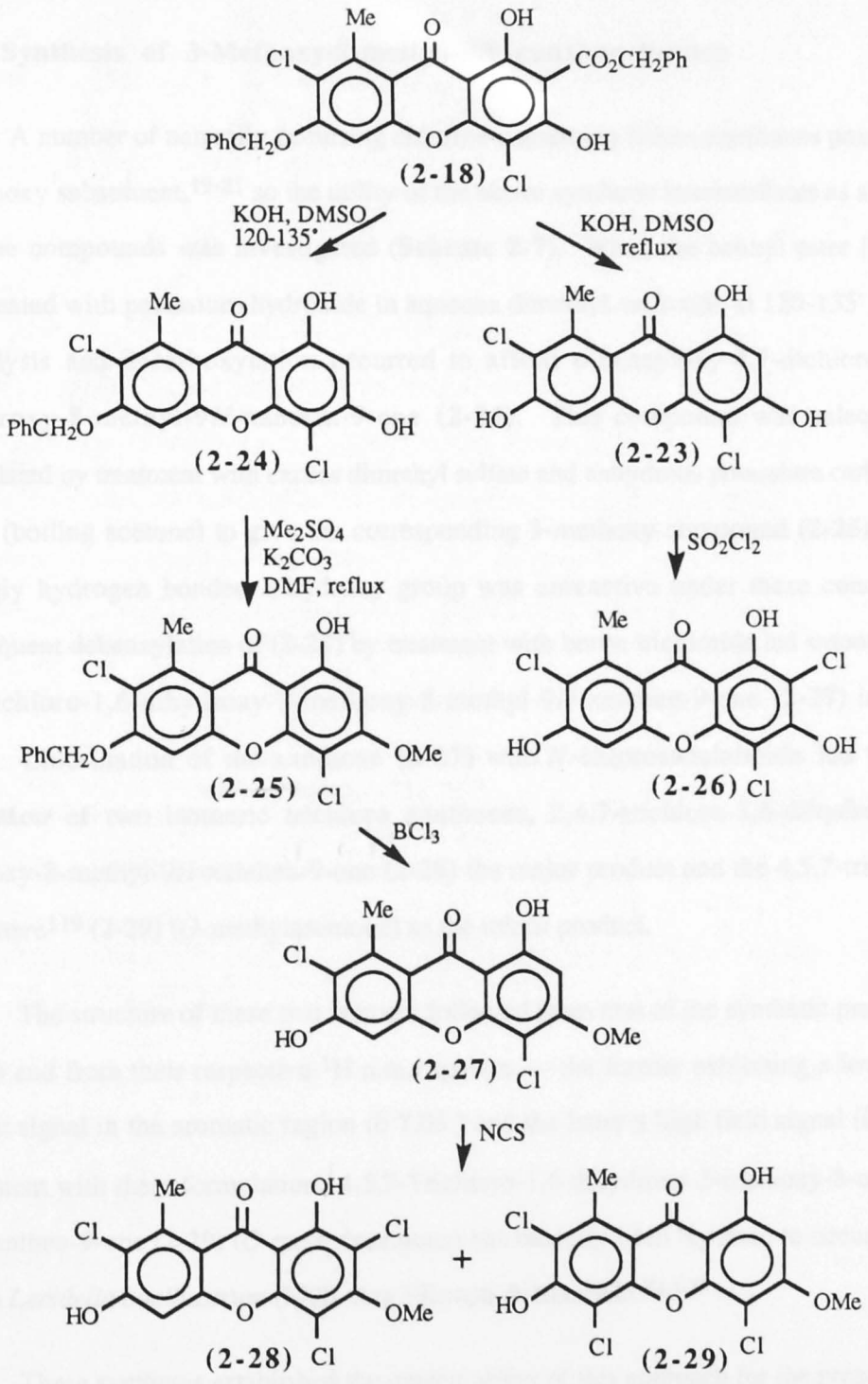
confirmed that in both cases, chlorination occurred in the B-ring (each exhibited a low-field singlet aromatic proton at δ 6.97 and 6.91 respectively, typical of an A-ring proton[51]). Moreover the structure of 4,7-dichloronorlichexanthone (**2-23**) was confirmed by unambiguous synthesis as described below (**Scheme 2-7**).

Thus the treatment of benzyl 6-benzyloxy-4,7-dichloro-1,3-dihydroxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylate (**2-18**) with potassium hydroxide in aqueous dimethyl sulfoxide at reflux effected ester hydrolysis, decarboxylation and *O*-debenzylation of the 6-benzyloxy group to afford 4,7-dichloronorlichexanthone (**2-23**) directly.

The synthesis of 2,4,7-trichloronorlichexanthone (**2-26**) was achieved by direct chlorination of 4,7-dichloronorlichexanthone (**2-23**) by treatment with sulfuryl chloride at room temperature (**Scheme 2-7**).

The structure of the 2,4,7-trichloro-compound (**2-26**) so-formed was confirmed by spectroscopic data. The molecular formula was established by high resolution mass spectrometry as $C_{14}H_7Cl_3O_5$. Further, the ^1H n.m.r. spectrum revealed a singlet low field aromatic peak at δ 6.96, typical of an A-ring proton (in this case H5).[51]

Thus this synthetic route proved a convenient new method for the unambiguous preparation of a variety of 4- and 7-chlorosubstituted xanthones.


Me
O
OH
Cl
CO2CH2Ph
PhCH2O
O
OH
(2-18)
Cl
KOH, DMSO
120-135°
KOH, DMSO
reflux
(2-24)
(2-23)
Me2SO4
K2CO3
DMF, reflux
SO2Cl2
(2-25)
(2-26)
BCl3
(2-27)
NCS
(2-28)
(2-29)
HO
OMe

Scheme 2-7

2.c. Synthesis of 3-Methoxy-8-methyl-9*H*-xanthen-9-ones

A number of naturally occurring chlorine-containing lichen xanthones possess a 3-methoxy substituent,[19-21] so the utility of the above synthetic intermediates as a route to these compounds was investigated (**Scheme 2-7**). When the benzyl ester (**2-18**) was treated with potassium hydroxide in aqueous dimethyl sulfoxide at 120-135°, ester hydrolysis and decarboxylation occurred to afford 6-benzyloxy-4,7-dichloro-1,3-dihydroxy-8-methyl-9*H*-xanthen-9-one (**2-24**). This compound was selectively methylated by treatment with excess dimethyl sulfate and anhydrous potassium carbonate at 58° (boiling acetone) to give the corresponding 3-methoxy compound (**2-25**). The strongly hydrogen bonded 1-hydroxy group was unreactive under these condition. Subsequent debenzylation of (**2-25**) by treatment with boron trichloride led smoothly to 4,7-dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one (**2-27**) in high yield. Chlorination of the xanthone (**2-27**) with *N*-chlorosuccinimide led to the formation of two isomeric trichloro xanthones, 2,4,7-trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one (**2-28**) the major product and the 4,5,7-trichloro derivative[119] (**2-29**) (*O*-methylasemone) as the minor product.

The structure of these two isomers followed from that of the synthetic precursor (**2-27**) and from their respective ^{1}H n.m.r.spectra — the former exhibiting a low field singlet signal in the aromatic region (δ 7.05) and the latter a high field signal (δ 6.50) consistent with these formulation. 4,5,7-Trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one (**2-29**) (*O*-methylasemone) has recently been reported to occur in the lichen *Lecidella buelliastrum* (Müll. Arg.) Knoph & Rambold.[82,100]

These syntheses established the overall utility of this approach for the preparation of substituted 3-methoxy-8-methyl-9*H*-xanthene-9-ones.

Chapter 3. Structure And Synthesis Of Norlichexanthones

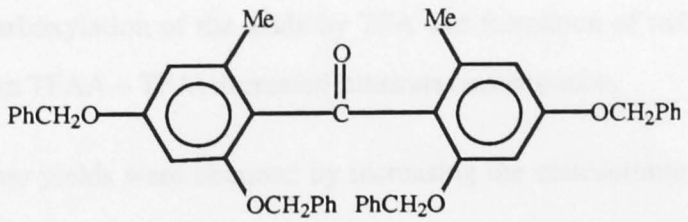
II. Friedel-Crafts Approach

3.a. Background

The use of Friedel-Crafts reactions in the synthesis of xanthones has been studied by Sundholm[120,122] and extended by Fitzpatrick and Sargent.[53] This method comprises several key steps. Initially an intermediate benzophenone is formed by *C*-acylation of an appropriately protected phloroglucinol derivative with a substituted orsellinic acid in the presence of trifluoroacetic anhydride (TFAA). Subsequent deprotection followed by cyclisation gave rise to the corresponding xanthone (see **Scheme 1-12**).

The mechanism for this acylation process in the presence of trifluoroacetic anhydride (TFAA) was proposed by Bourne et al.[8-11] and Randles et al.[101] The formation of acylium ions ($ArCO^+$) from the acyl trifluoroacetates formed in the first step of the reaction is responsible for the acylation.

Sundholm[120,121] conducted a detailed investigation into the various aspects of this reaction and isolated symmetrical benzophenones (e.g. (**3-1**)) as the main by-products. He suggested a possible mechanism for formation of such symmetrical



(3-1)

benzophenones as outlined in **Scheme 3-1**. The expected benzophenone (**3-2**) may react with TFA (trifluoroacetic acid) to form the protonated intermediate (**3-3**) and hence the neutral intermediate (**3-4**). Further protonation of this intermediate and subsequent elimination of the mononuclear moieties (**3-7**) and (**3-8**) would produce the unsymmetrical anhydrides (**3-6**) and (**3-9**). The anhydrides (**3-6**) and (**3-9**) could then react with aromatic substrates released to form the observed by-products, namely the symmetrical benzophenones (**3-10**) and (**3-11**). In summary, Sundholm concluded that:

1) The reactivity of the acid moiety (and acyl trifluoroacetate) increased on substitution with chloro substituents.

2) The reactivity of the aromatic ether decreased on nuclear chlorination and no reaction was observed if the substituents interfered with the reaction site.

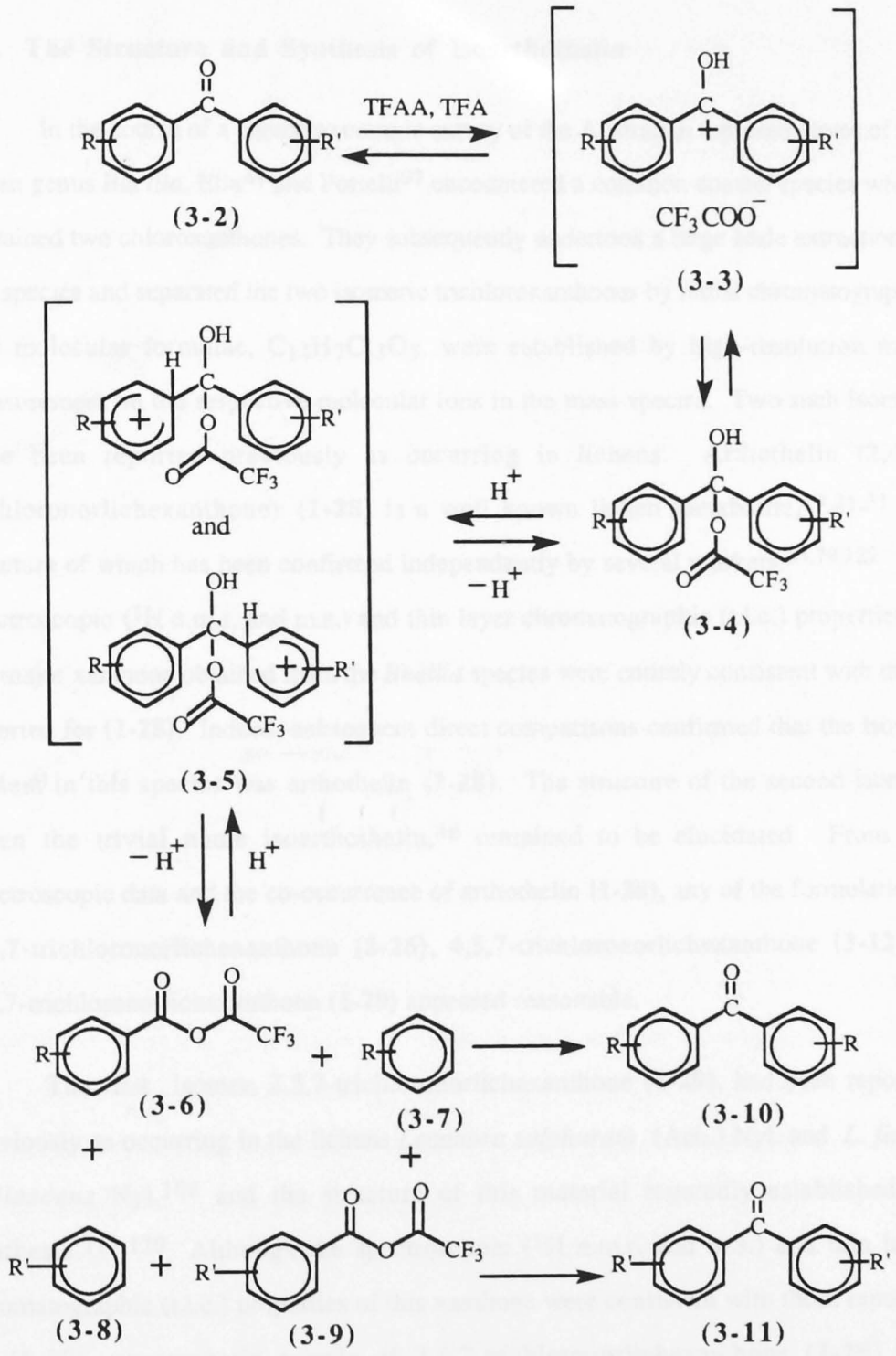
3) The reaction took an alternative path when substituents in the acid caused steric crowding of the reaction site (the carbonyl function) and symmetrical anhydrides resulted. This side reaction was inhibited by conducting the acylation at lower temperature or by the addition of trifluoroacetic acid (TFA).

4) The formation of symmetrical benzophenones was slower than the acylation reaction although both reaction were catalyzed by TFA.

5) Decarboxylation of the acids by TFA and formation of trifluoroacetylated compounds (from TFAA + TFA) decreased substrate concentration.

6) Higher yields were obtained by increasing the concentration of one of the substrates.

This method is particularly useful in the synthesis of 2-chlorolichexanthones, which could not be synthesized unambiguously by utilizing the Smiles rearrangement.



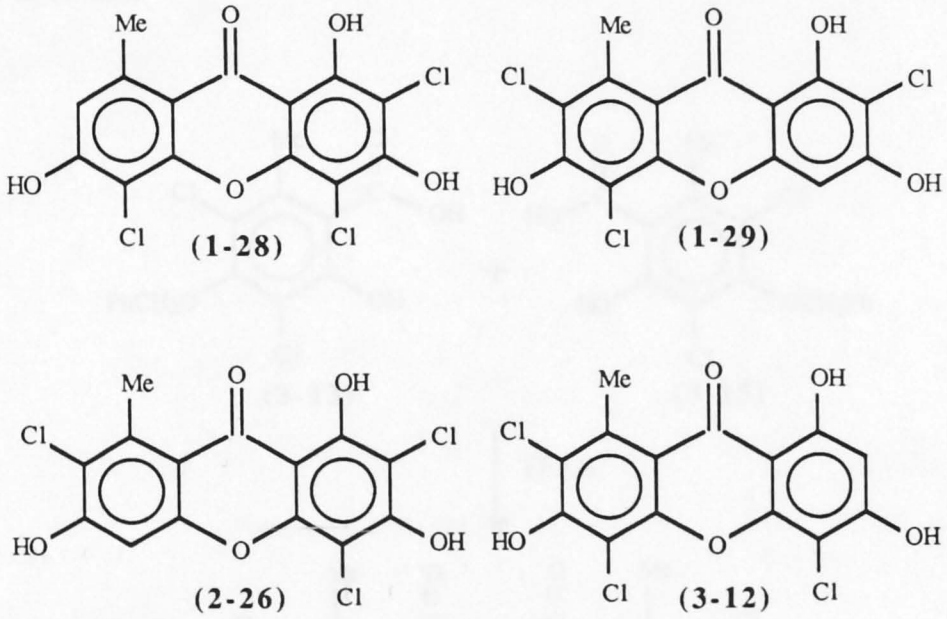
Scheme 3-1

3.b. The Structure and Synthesis of Isoarthothelin

In the course of a chemotaxonomic survey of the Australian representatives of the lichen genus *Buellia*, Elix[44] and Portelli[97] encountered a common coastal species which contained two chloroxanthones. They subsequently undertook a large scale extraction of this species and separated the two isomeric trichloroxanthones by radial chromatography. The molecular formulae, $C_{14}H_7Cl_3O_5$, were established by high-resolution mass measurement on the respective molecular ions in the mass spectra. Two such isomers have been reported previously as occurring in lichens. Arthothelin (2,4,5-trichloronorlichexanthone) **(1-28)** is a well known lichen metabolite,[19,21,51] the structure of which has been confirmed independently by several workers.[53,79,122] The spectroscopic (^{1}H n.m.r. and m.s.) and thin layer chromatographic (t.l.c.) properties of the major xanthone obtained from the *Buellia* species were entirely consistent with those reported for **(1-28)**. Indeed, subsequent direct comparisons confirmed that the isomer present in this species was arthothelin **(1-28)**. The structure of the second isomer, given the trivial name isoarthothelin,[46] remained to be elucidated. From the spectroscopic data and the co-occurrence of arthothelin **(1-28)**, any of the formulations, 2,4,7-trichloronorlichexanthone **(2-26)**, 4,5,7-trichloronorlichexanthone **(3-12)** or 2,5,7-trichloronorlichexanthone **(1-29)** appeared reasonable.

The last isomer, 2,5,7-trichloronorlichexanthone **(1-29)**, had been reported previously as occurring in the lichens *Lecanora sulphurata* (Ach.) Nyl. and *L. flavo-pallescens* Nyl.[108] and the structure of this material reputedly established by synthesis.[119,120] Although the spectroscopic (^{1}H n.m.r. and m.s.) and thin layer chromatographic (t.l.c.) properties of this xanthone were consistent with those reported for **(1-29)**, no synthetic sample of 2,5,7-trichloronorlichexanthone **(1-29)** was available for comparison. However, the lichens reported to contain **(1-29)** were available, but high-performance liquid chromatographic (h.p.l.c.) comparisons showed

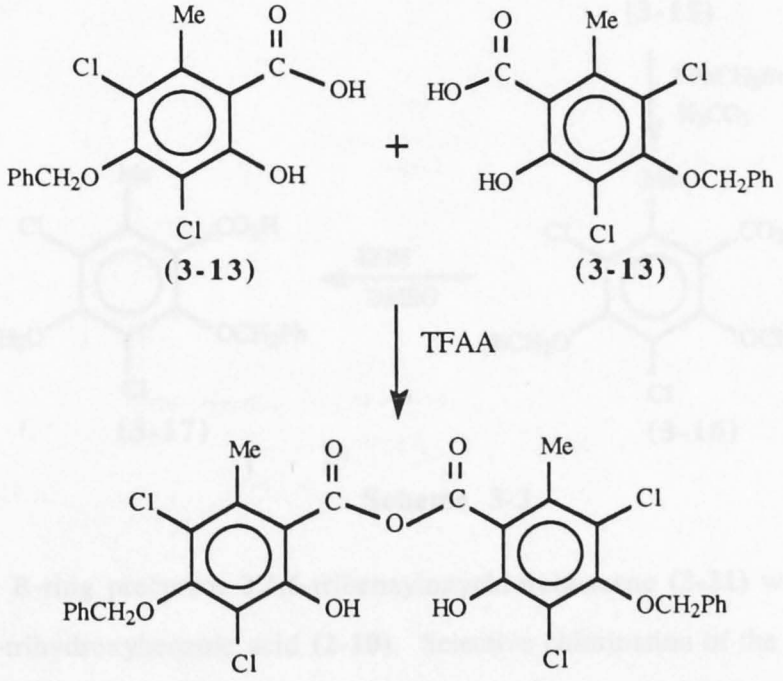
that the minor isomer from the *Buellia* species (isoarthothelin) was not present in *L. flavo-pallescens*. In an attempt to resolve this apparent anomaly, 2,4,7-trichloronorlichexanthone **(2-26)** and 2,5,7-trichloronorlichexanthone (isoarthothelin)



(1-29) were synthesized in the present work (see **Schemes 2-7** and **3-5**) in order to make direct comparisons possible. Subsequent chromatographic comparisons (t.l.c., h.p.l.c.) showed that the synthetic 2,4,7-trichloronorlichexanthone **(2-26)** was dissimilar to natural isoarthothelin, but was present in *L. flavo-pallescens* (see section **3.e.**). Isoarthothelin has also been shown to occur in *L. broccha* Nyl.,[43] another Austral lichen.

Attempts to use a Smiles approach in the synthesis of 2,5,7-trichloronorlichexanthone **(1-29)** failed as the initial condensation of 4-benzyloxy-3,5-dichloro-2-hydroxy-6-methylbenzoic acid **(3-13)** with benzyl 2,4,6-trihydroxybenzoate

(**2-11**) yielded only traces of the required depside. Most probably competitive formation of the symmetrical anhydride (**3-14**) in this reaction was responsible for this result (**Scheme 3-2**). Similar problems have been encountered previously[119,120] and rationalised in terms of the steric influence of the chloro substituents in the acid — in this case in (**3-13**).



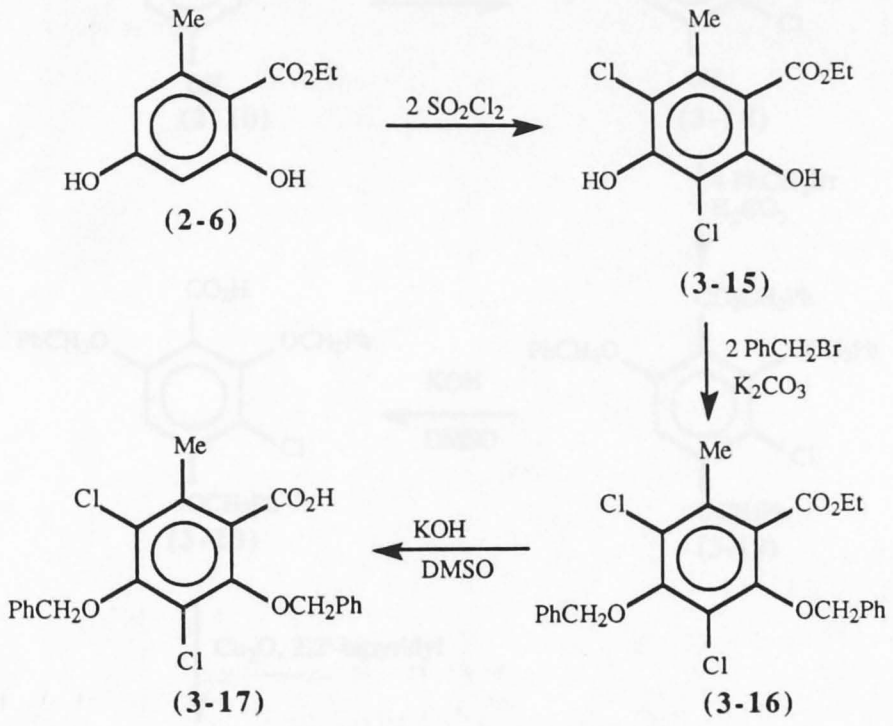
(**3-13**) + (**3-13**)

(**3-14**)

Scheme 3-2

Consequently an alternative, more direct, modified Friedel-Crafts approach[53,122] to this compound was undertaken via the route outlined in **Scheme 3-5**. Two key mononuclear prscursors were required and their preparation is outlined in **Schemes 3-3** and **3-4**. The acid (**3-17**) was prepared by minor modifications of the reported

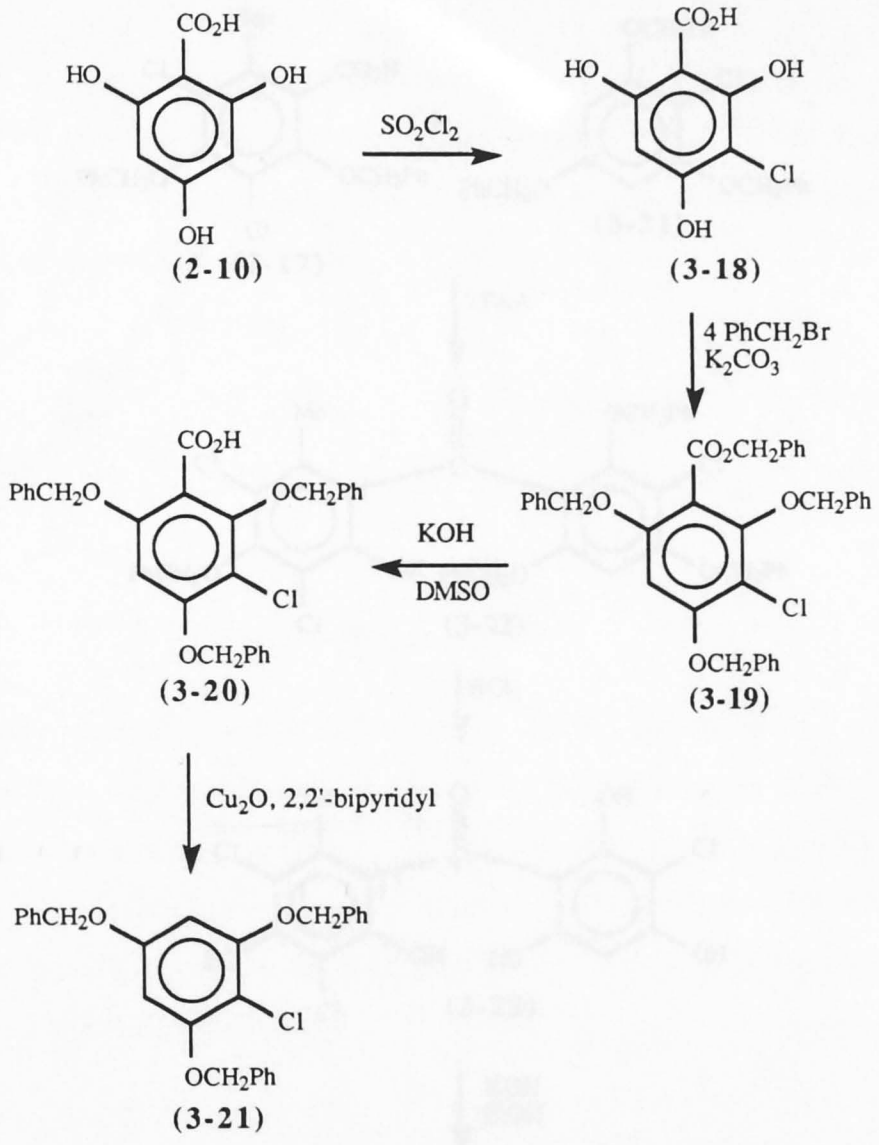
literature method.[53,122] Starting from ethyl orsellinate (**2-6**) sequential chlorination, benzylation and hydrolysis gave the required acid (**3-17**).



Scheme 3-3

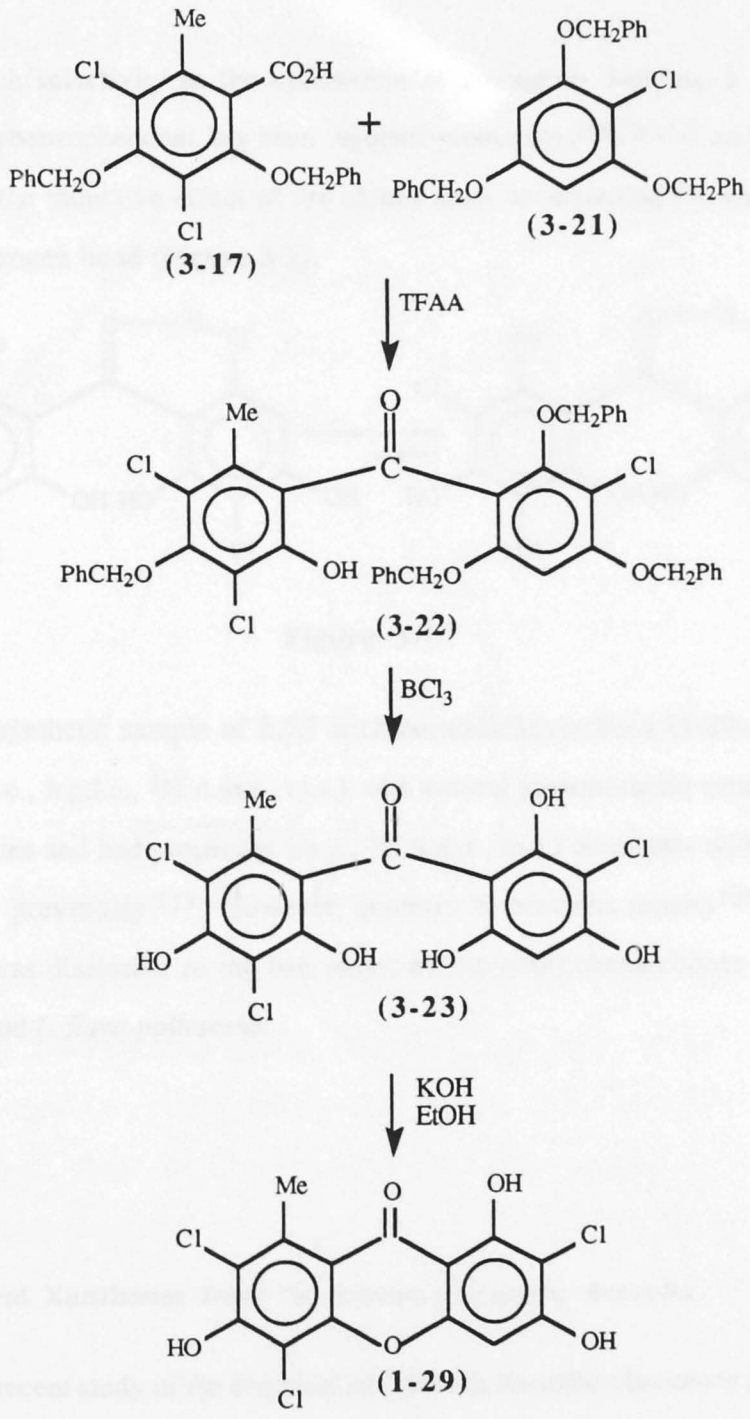
The B-ring precursor 2,4,6-tribenzyloxychlorobenzene (**3-21**) was prepared from 2,4,6-trihydroxybenzoic acid (**2-10**). Selective chlorination of the acid (**2-10**) with one mole of sulfuryl chloride gave the product (**3-18**) which upon treatment with excess benzyl bromide in the presence of anhydrous potassium carbonate effected perbenzylation to afford benzyl 2,4,6-tribenzyloxy-3-chlorobenzoate (**3-19**). This compound was then subjected to alkaline hydrolysis and the acid (**3-20**) so formed was decarboxylated by treatment with cuprous oxide and 2,2'-bipyridyl in boiling dimethylformamide to afford the required 1,3,5-tribenzyloxy-2-chlorobenzene (**3-21**).

The condensation between the acid (**3-17**) and 2,4,6-tribenzyloxychlorobenzene (**3-21**) in the presence of trifluoroacetic anhydride gave the benzophenone (**3-22**).



Scheme 3-4

Partial debenzylation accompanied this condensation — apparently catalysed by the trifluoroacetic acid produced in the initial step. Boron trichloride effected complete debenzylation of the benzophenone (**3-22**) to give the crude pentahydroxybenzophenone (**3-23**). On boiling in ethanolic potassium hydroxide (**3-23**) underwent selective cyclisation[53,120,122] to give 2,5,7-trichloronorlichexanthone


Me
Cl
CO2H
PhCH2O
OCH2Ph
Cl
(3-17)
+
OCH2Ph
Cl
PhCH2O
OCH2Ph
(3-21)
TFAA
O
C
Me
Cl
PhCH2O
OH
Cl
OCH2Ph
Cl
PhCH2O
OCH2Ph
(3-22)
BCl3
Me
OH
HO
OH
(3-23)
KOH
EtOH
(1-29)

Scheme 3-5

(**1-29**). Such selectivity in the cyclisation of analogous 3-chloro-2, 2', 4, 4', 6-pentahydroxybenzophenones has been reported previously,[119,120,122] and is reputedly due to an *ortho* inductive effect of the chloro atom accentuating the strength of the adjacent hydrogen bond (**Figure 3-1**).

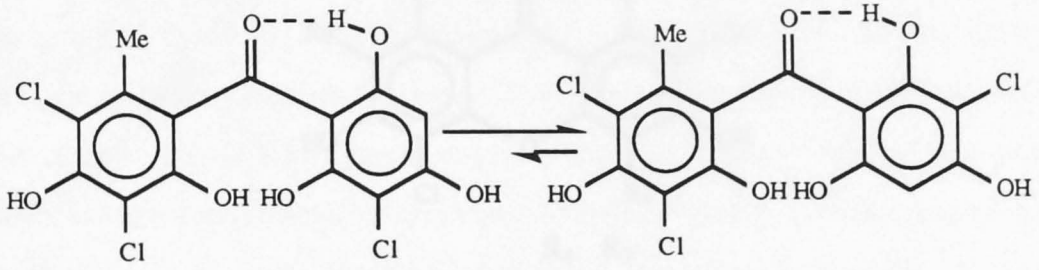


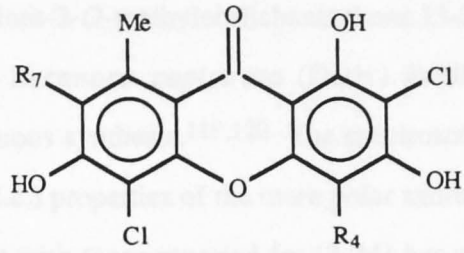
Figure 3-1

The synthetic sample of 2,5,7-trichloronorlichexanthone (**1-29**) proved to be identical (t.l.c., h.p.l.c., ^{1}H n.m.r., m.s.) with natural isoarthothelin isolated from the *Buellia* species and had properties (m.p., ^{1}H n.m.r., m.s.) consistent with the material synthesized previously.[119] However, contrary to previous reports[108,119,120] this compound was dissimilar to the two major trichloronorlichexanthones present in *L. sulphurata* and *L. flavo-pallescens*.

3.c. Natural Xanthones from the Lichen *Lecanora broccha*

In a recent study of the chemical variation in the lichen *Lecanora broccha*, Elix, Jenkin and Lumbsch[43] reported the presence of two major, unidentified xanthones as

well as the sporadic occurrence of traces of the known xanthones, arthothelin **(1-28)**,[#] isoarthothelin **(1-29)** and thiophanic acid **(1-30)**. Although these new xanthones were detected by thin layer (t.l.c.) and high performance liquid chromatography (h.p.l.c.), they were not isolated or studied chemically.



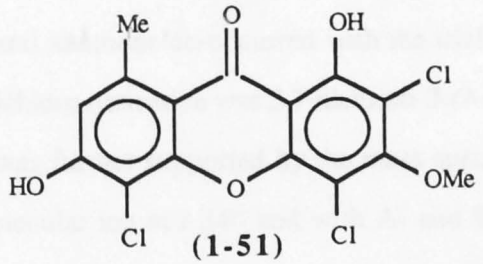
	R_4	R_7
(1-28)	Cl	H
(1-29)	H	Cl
(1-30)	Cl	Cl

The present work describes the isolation, purification, structural elucidation and synthesis of the two major xanthones present in *L. broccha* .

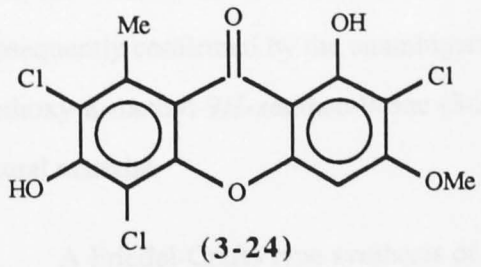
After a large scale extraction of this species, the two major xanthones were separated by radial chromatography. The major, more polar xanthone was shown to have the molecular formula $C_{15}H_9Cl_3O_5$ by high resolution mass measurement of the molecular ion. Three such isomers have been reported previously as occurring in lichens. Thuringione (2,4,5-trichloro-3-*O*-methylnorlichexanthone) **(1-51)** is a well known lichen metabolite,[19,21,51] the structure of which has been confirmed independently by several workers.[53,79,120,122] 4,5,7-Trichloro-3-*O*-

[#] This compound was recorded[43] as xanthone X-4, but was subsequently shown to be identical with arthothelin

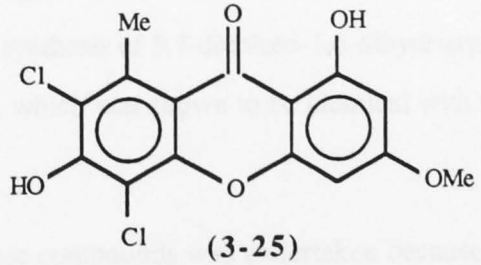
methylnorlichexanthone **(2-29)** (3-*O*-methylasemone) has recently been reported to occur in the lichen *Lecidella buelliastrum* (Müll. Arg.) Knoph & Rambold,[82,100] but this alternative was discounted by direct comparison of the natural xanthone from *L. broccha* with authentic material of **(2-29)** synthesised previously (see section **2.c.**). A third isomer, 2,5,7-trichloro-3-*O*-methylnorlichexanthone **(3-24)**, has been reported as occurring in the lichen *Lecanora capistrata* (Darb.) Zahlbr.[108] and the structure established by unambiguous synthesis.[119,120] The spectroscopic (^{1}H n.m.r. and m.s.) and chromatographic (t.l.c.) properties of the more polar xanthone obtained from the *L. broccha* were consistent with those reported for **(3-24)** but no synthetic material was available for comparison. Demethylation of the natural xanthone by treatment with boron tribromide afforded isoarthothelin **(1-29)**, thus confirming the 2,5,7-trichloro substitution of this derivative. Indeed 2,5,7-trichloro-3-*O*-methylnorlichexanthone **(3-24)** was resynthesised (see below) and direct comparisons confirmed that these two compounds were indentical.



(1-51)



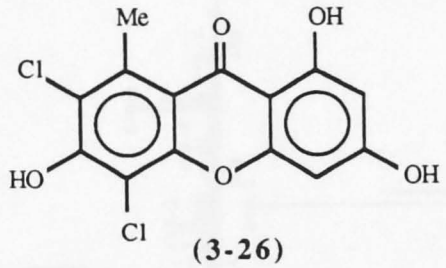
(3-24)



(3-25)

The minor, less polar xanthone present in *L. broccha* was found to be a derivative of dichloro-*O*-methylnorlichexanthone. Thus high resolution mass spectrometry

established the molecular formula of this xanthone as $C_{15}H_{10}Cl_2O_5$. The ^1H n.m.r. spectrum showed a *C*-methyl resonance (δ 2.82), an *O*-methyl signal (δ 3.85), two aromatic signals (δ 6.24, 6.42, *J* 2.1Hz) and a downfield hydroxy signal (δ 14.00). The chemical shift of the *C*-methyl signal was consistent with that expected for a 7-chloronorlichexanthone,[120,122] where the adjacent chloro atom deshields these protons. Further, the chemical shift and *meta*-coupling observed for the aromatic protons, indicated that this compound was probably a derivative of 5,7-dichloronorlichexanthone. This substitution pattern was confirmed by demethylation of this xanthone to afford 5,7-dichloronorlichexanthone **(3-26)**. Authentic **(3-26)** has been synthesized recently by

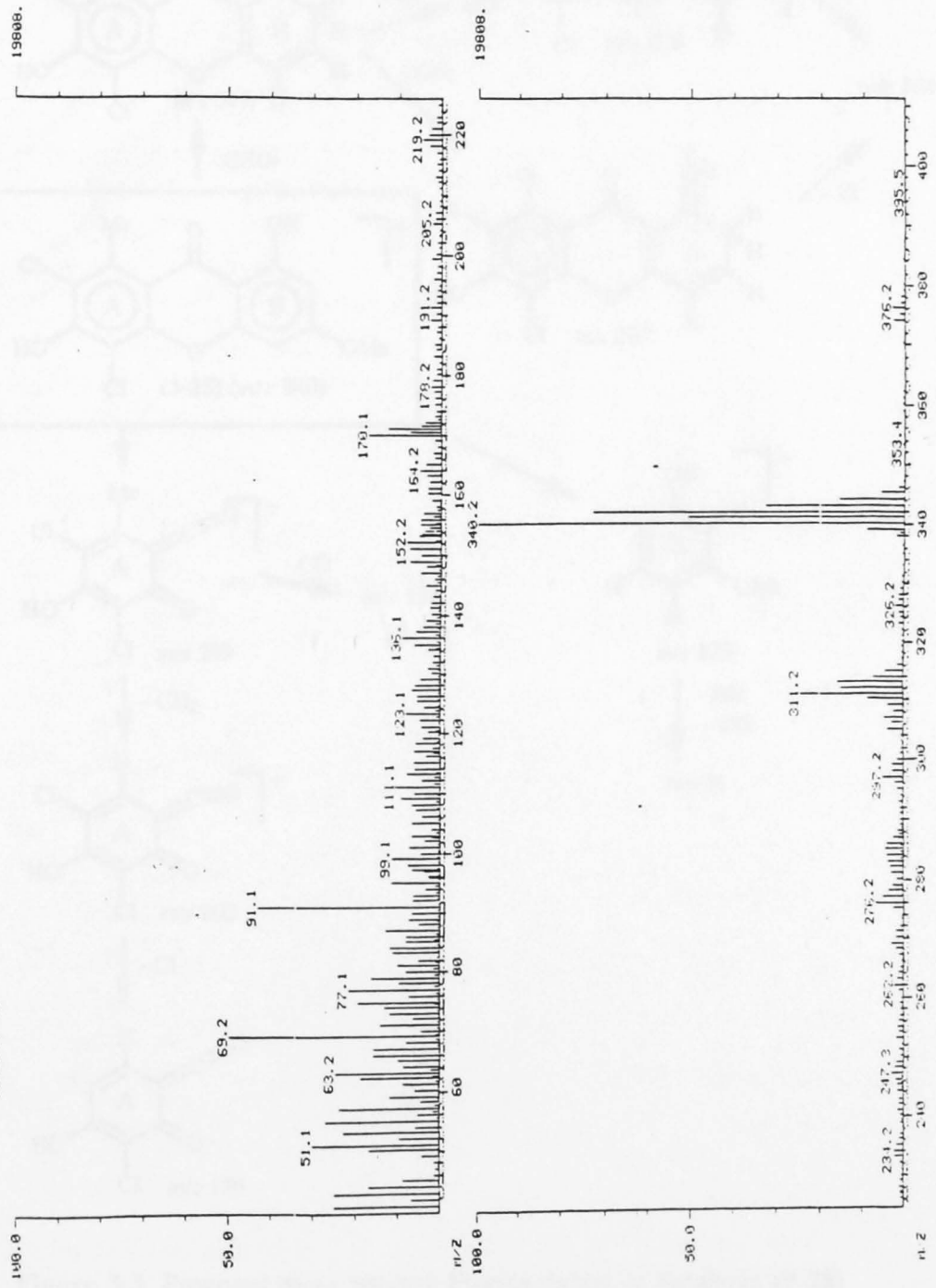


(3-26)

Elix et al.[37] As the natural xanthone co-occurred with the trichloroxanthone **(3-24)**, it seemed likely that this dichloro derivative was 5,7-dichloro-3-*O*-methylnorlichexanthone **(3-25)**. This postulate was further supported by the mass spectrum of this compound (**Figure 3-2**) with a molecular ion *m/z* 340 and with A- and B-ring fragments at *m/z* 219 and 123 respectively. All the observed fragment ions could be rationalised as arising from the structure **(3-25)** as illustrated in **Figure 3-3**. The structure of **(3-25)** was subsequently confirmed by the unambiguous synthesis of 5,7-dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one **(3-25)**, which was shown to be identical with the natural material.

A Friedel-Crafts type synthesis of these compounds was undertaken because of the tendency for the precursor **(3-13)** to undergo self-condensation in the presence of

Figure 3-2. Mass Spectrum of Xanthone (**3-25**)



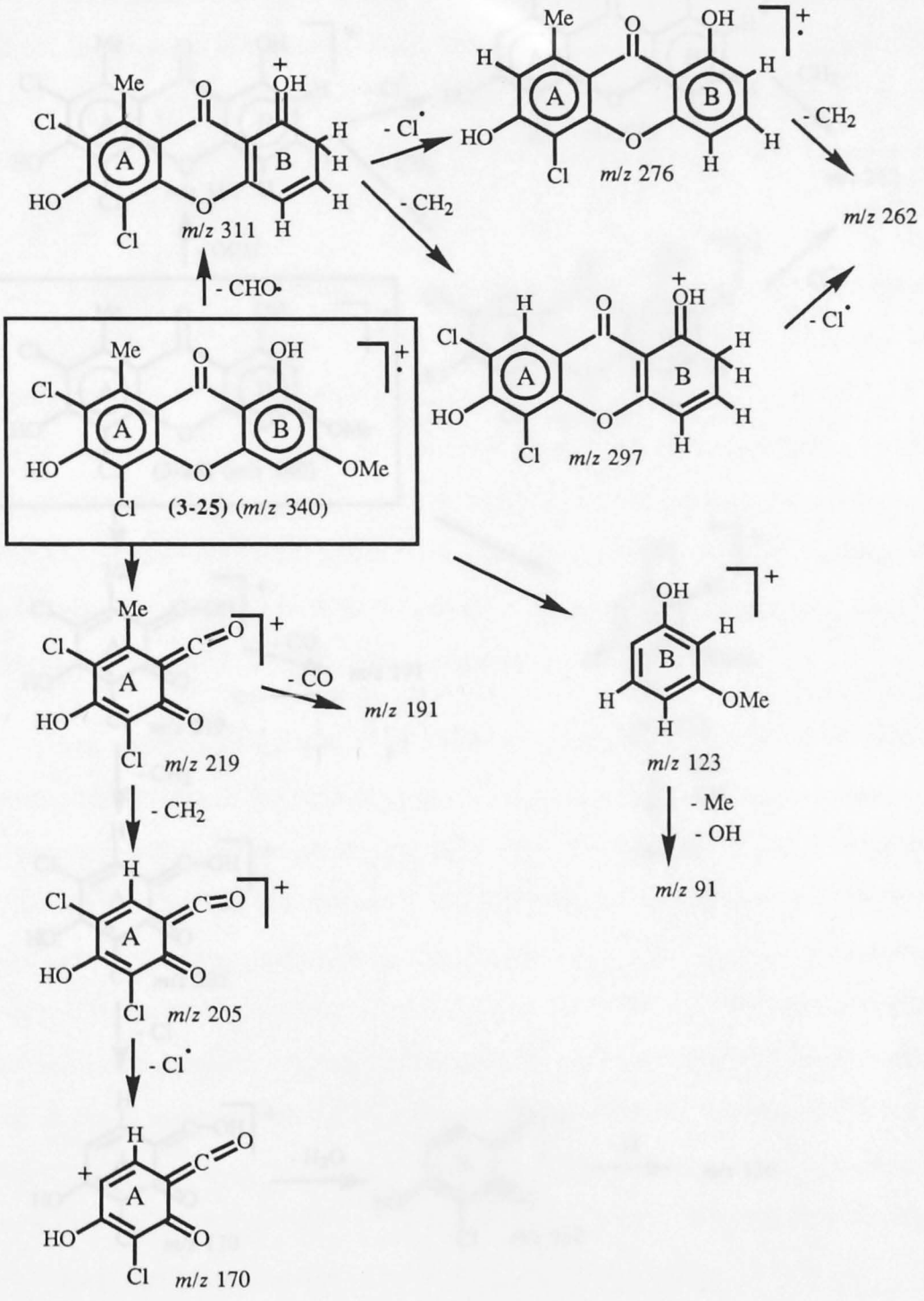
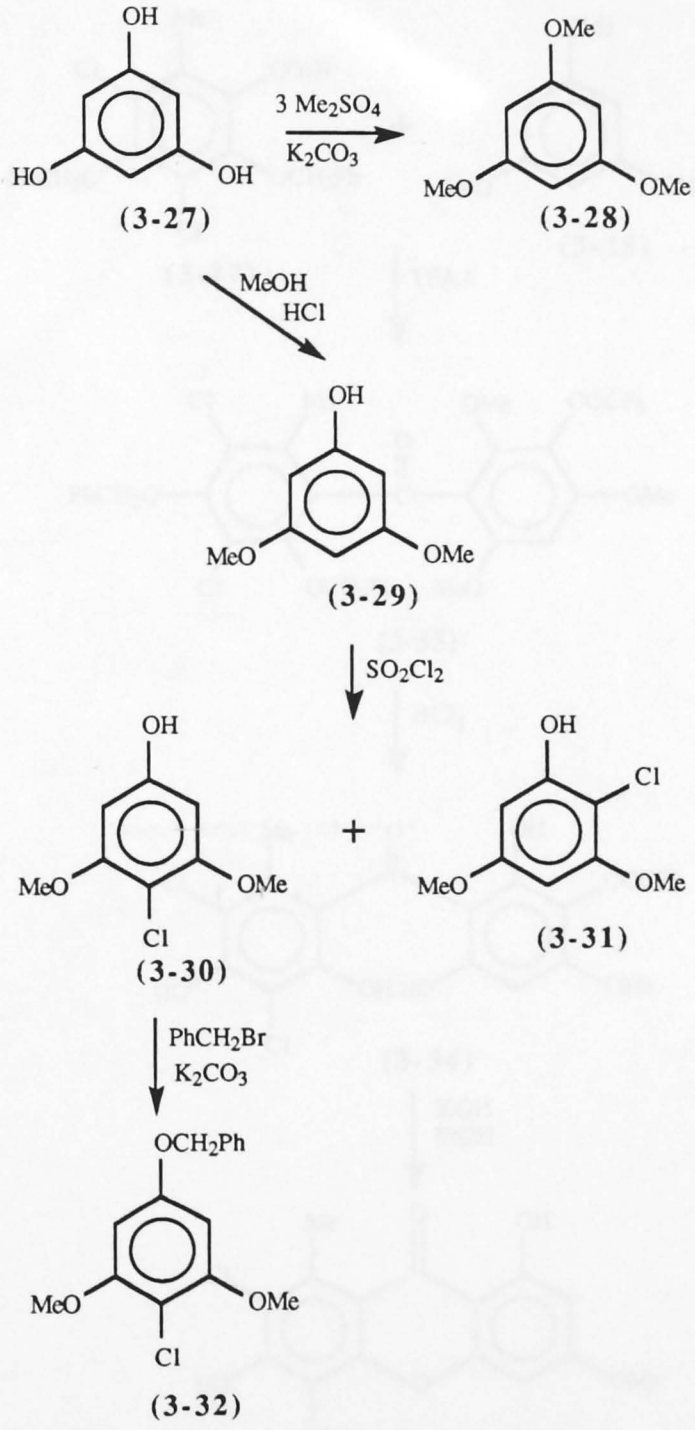


Figure 3-3 Proposed Mass Spectral Fragmentation of Xanthone (**3-25**)

trifluoroacetic anhydride (see section **3.b.** above). The synthetic routes used are outlined in **Schemes 3-7** and **3-8**, while the key mononuclear precursors **(3-28)** and **(3-32)** were prepared as showed in **Scheme 3-6**. The synthetic route to 2,5,7-trichloro-3-*O*-methylnorlichexanthone **(3-24)** was analogous to that described previously by Sundholm.[119]

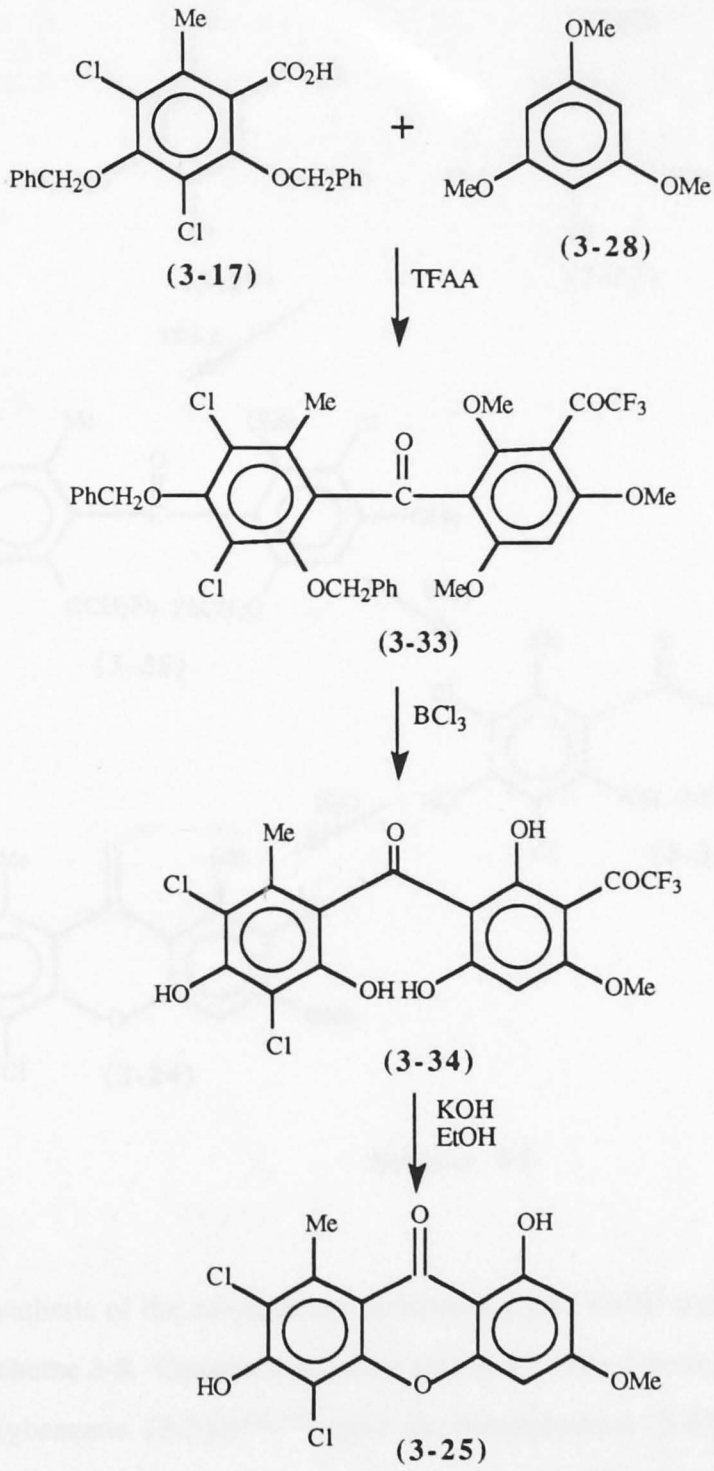
Phloroglucinol **(3-27)** was fully methylated by treatment with excess dimethyl sulfate and potassium carbonate to yield 1,3,5-trimethoxybenzene **(3-28)**. Alternatively phloroglucinol was treated with methanol and hydrochloric acid to yield 3,5-dimethoxyphenol **(3-29)** which in turn underwent chlorination by treatment with sulfuryl chloride to afford the two isomers, 4-chloro-3,5-dimethoxyphenol **(3-30)** and 2-chloro-3,5-dimethoxyphenol **(3-31)**.[57] After purification by flash chromatography[116] the former was benzylated with benzyl bromide and potassium carbonate to afford 5-benzyloxy-2-chloro-1,3-dimethoxybenzene **(3-32)** in a high yield.

Condensation of the acid **(3-17)** with 1,3,5-trimethoxybenzene **(3-28)** in the presence of trifluoroacetic anhydride gave the benzophenone **(3-33)**, where subsequent trifluoroacetylation further substituted the B-ring. Treatment of **(3-33)** with boron trichloride afforded the hydroxybenzophenone **(3-34)**, and subsequent base-induced ring closure also effected hydrolytic de-trifluoroacetylation to give the required xanthone **(3-25)**. This material was identical (t.l.c., h.p.l.c., ^{1}H n.m.r., m.s.) with the less polar xanthone isolated from *L. broccha* . Minor quantities of this xanthone **(3-25)** have also been shown to co-occur with 2,5,7-trichloro-3-*O*-methylnorlichexanthone **(3-24)** in *L. capistrata* (rather than the isomeric compound, thiophaninic acid **(1-53)**, as had previously been suggested[119]). The compound **(3-25)** was the first natural norlichexanthone known to exhibit a 5,7-dichloro-substitution pattern.

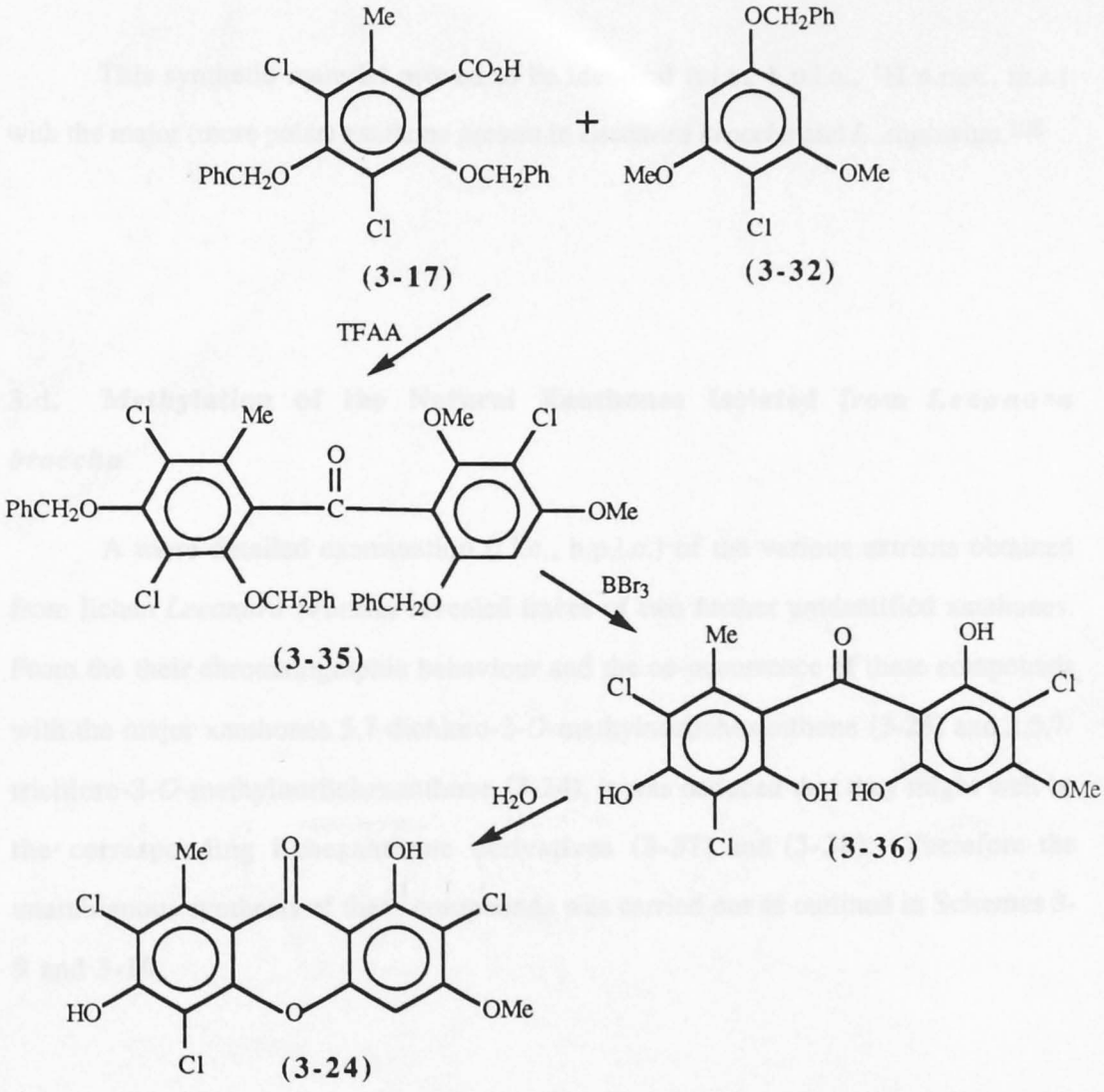


(3-27) **(3-28)** **(3-29)** **(3-30)** **(3-31)** **(3-32)**

Scheme 3-6


Me
Cl
CO2H
PhCH2O
OCH2Ph
Cl
(3-17)
+
OMe
MeO
OMe
(3-28)
TFAA
Cl
Me
OMe
COCF3
O
PhCH2O
C
OMe
Cl
OCH2Ph
MeO
(3-33)
BCl3
Me
O
OH
Cl
COCF3
HO
OH HO
OMe
Cl
(3-34)
KOH
EtOH
Me
O
OH
Cl
HO
O
OMe
Cl
(3-25)

Scheme 3-7



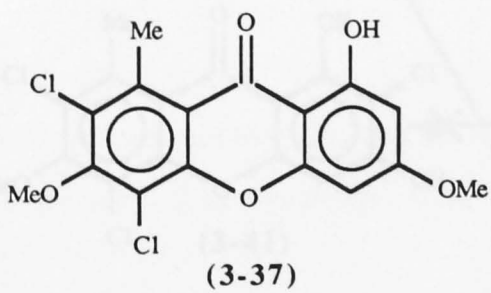
Scheme 3-8

The synthesis of the co-occurring trichloroxanthone **(3-24)** was carried out as depicted in **Scheme 3-8**. Condensation of the acid **(3-17)** with 5-benzyloxy-2-chloro-1,3-dimethoxybenzene **(3-32)**[109,119] gave the benzophenone **(3-35)** and then the hydroxybenzophenone **(3-36)**. This compound underwent selective ring closure (see section **3.b.**) in boiling water to give the xanthone **(3-24)**.

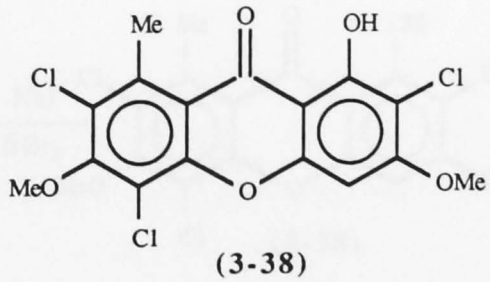
This synthetic material proved to be identical (t.l.c., h.p.l.c., ^{1}H n.m.r., m.s.) with the major (more polar) xanthone present in *Lecanora broccha* and *L. capistrata*.[108]

3.d. Methylation of the Natural Xanthones Isolated from *Lecanora broccha*

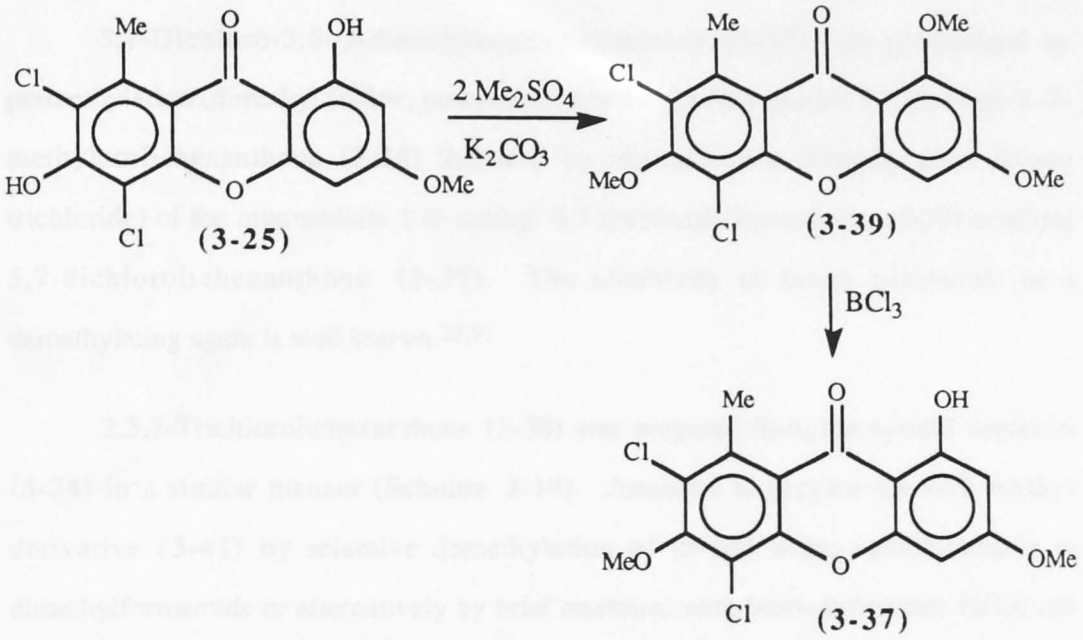
A more detailed examination (t.l.c., h.p.l.c.) of the various extracts obtained from lichen *Lecanora broccha* revealed traces of two further unidentified xanthones. From the their chromatographic behaviour and the co-occurrence of these compounds with the major xanthones 5,7-dichloro-3-*O*-methylnorlichexanthone (**3-25**) and 2,5,7-trichloro-3-*O*-methylnorlichexanthone (**3-24**), it was deduced that they might well be the corresponding lichexanthone derivatives (**3-37**) and (**3-38**). Therefore the unambiguous synthesis of these compounds was carried out as outlined in **Schemes 3-9** and **3-10**.



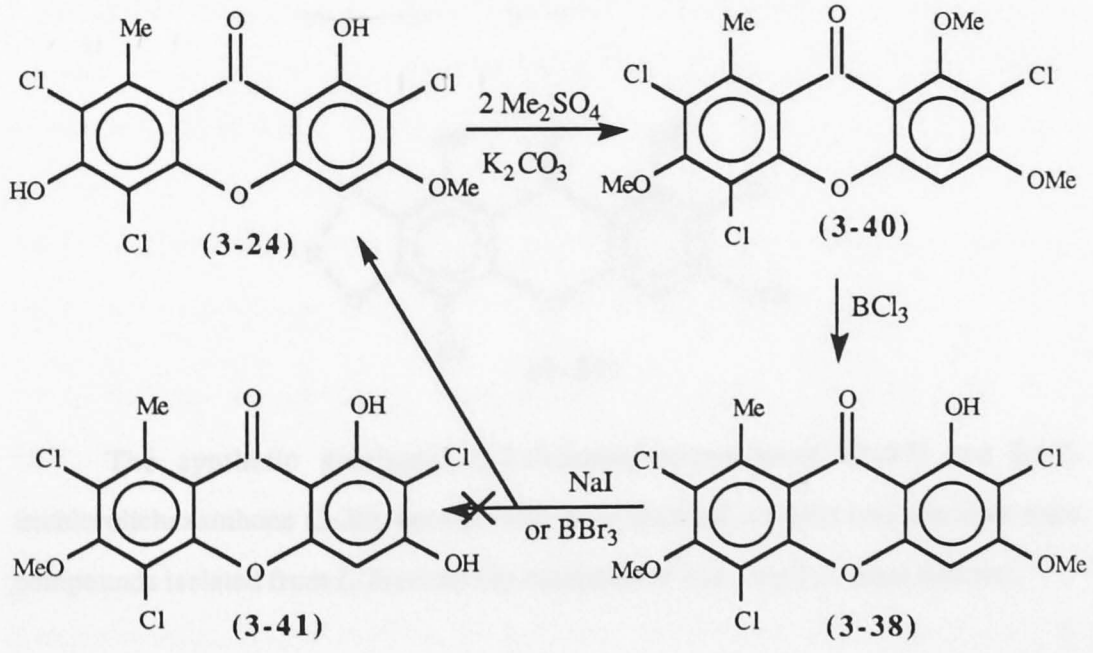
(3-37)



(3-38)



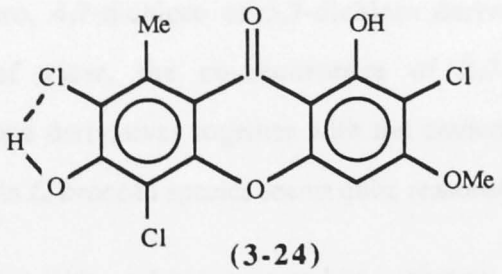
Scheme 3-9



Scheme 3-10

5,7-Dichloro-3,6-*O*-dimethylnorlichexanthone (**3-37**) was synthesized by permethylation (dimethyl sulfate, potassium carbonate) of the natural 5,7-dichloro-3-*O*-methylnorlichexanthone (**3-25**) followed by regioselective demethylation (boron trichloride) of the intermediate 1-*O*-methyl-5,7-dichlorolichexanthone (**3-39**) to afford 5,7-dichlorolichexanthone (**3-37**). The selectivity of boron trichloride as a demethylating agent is well known.[23,97]

2,5,7-Trichlorolichexanthone (**3-38**) was prepared from the natural xanthone (**3-24**) in a similar manner (**Scheme 3-10**). Attempts to prepare the 6-*O*-methyl derivative (**3-41**) by selective demethylation of (**3-38**) using sodium iodide in dimethylformamide or alternatively by brief treatment with boron tribromide failed and only the 3-*O*-methyl compound (**3-24**) and isoarthothelin (**1-29**) were obtained. We attributed this observed selectivity to hydrogen bonding between 6-hydroxy hydrogen and the adjacent chlorine preferentially stabilising the product (**3-24**).



(3-24)

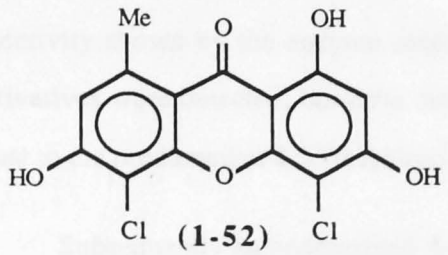
The synthetic xanthones 5,7-dichlorolichexanthone (**3-37**) and 2,5,7-trichlorolichexanthone (**3-38**) were showed to be identical with the two unknown trace compounds isolated from *L. broccha* (by comparative t.l.c., h.p.l.c., mass spectra).

3.e. Natural Occurrence of New Norlichexanthone Derivatives

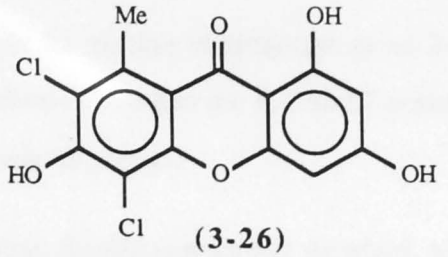
Direct comparisons (t.l.c., h.p.l.c.) showed that 2,7-dichloronorlichexanthone (**2-22**) occurred as a minor component in a specimen of *Lecanora broccha* from Argentina, together with four other xanthones, 5,7-dichloronorlichexanthone (**3-26**),[37] 5,7-dichloro-3-*O*-methylnorlichexanthone (**3-25**), 2,5,7-trichloro-3-*O*-methylnorlichexanthone (**3-24**), and isoarthothelin (**1-29**) (**Figure 3-4**). This is the first reported natural occurrence of 2,7-dichloronorlichexanthone (**2-22**) and 5,7-dichloronorlichexanthone (**3-26**).

As the penultimate processes in the biosynthesis of such chlorinated norlichexanthone derivatives involve nuclear chlorination and / or *O*-methylation steps, the pattern of co-occurring xanthones should constitute a coherent array of major xanthones and satellite derivatives. For instance, in a species with arthothelin (2,4,5-trichloronorlichexanthone, (**1-28**)), as the major component, one would anticipate trace amounts of 2,4-dichloro, 2,5-dichloro and 4,5-dichloro derivatives, but would not expect any 2,7-dichloro, 4,7-dichloro or 5,7-dichloro derivatives. Thus from a biosynthetic point of view, the co-occurrence of 2,7-dichloro- and 5,7-dichloronorlichexanthone derivatives together with the predominant 2,5,7-trichloro-substituted compounds in *L. broccha* species seems quite reasonable.

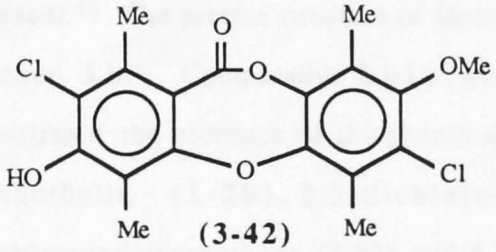
Further comparative chromatographic studies showed that 5,7-dichloronorlichexanthone (**3-26**) was also a minor component of the lichen *Lecidella subalpicida*, co-occurring with two depsidones, vicanicin (**3-42**), *O*-methylvicanicin (**3-43**), and three xanthones, isoarthothelin (**1-29**), 5,7-dichloro-3-*O*-methylnorlichexanthone (**3-25**) and 2,5,7-trichloro-3-*O*-methylnorlichexanthone (**3-24**). However no trace of either 2,7-dichloro or 4,7-dichloro derivatives was found in this species.



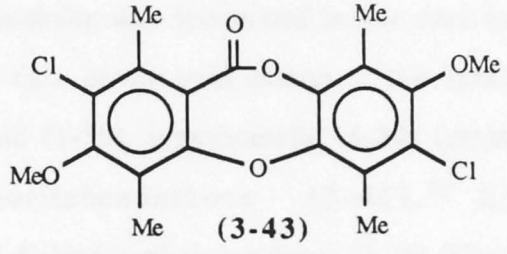
(1-52)



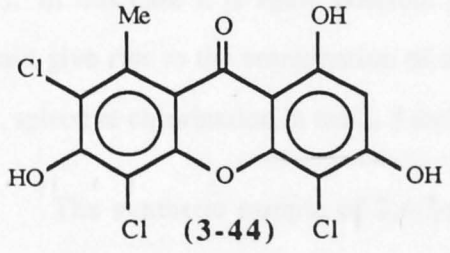
(3-26)



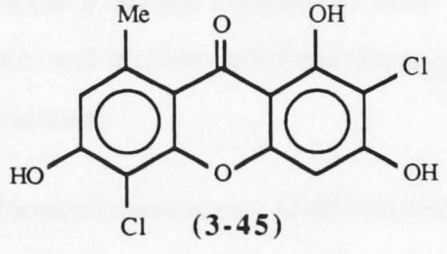
(3-42)



(3-43)



(3-44)



(3-45)

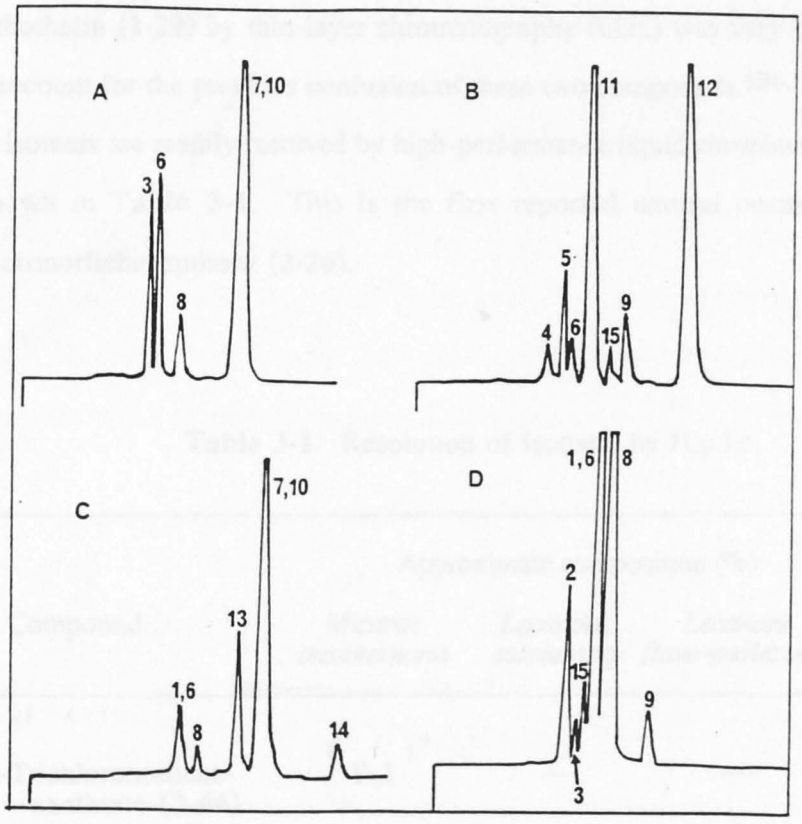
A third species, *Lecidella asema*, was also shown to contain a significant array of dichloronorlichexanthone derivatives. Comparative h.p.l.c. and t.l.c. of the total extract of this lichen (**Figure 3-4**) confirmed the presence of 4,5,7-trichloro-3-*O*-methylnorlichexanthone (**2-29**), 4,5,7-trichloronorlichexanthone (asemone) (**3-44**),[45] thiophanic acid (**1-30**), 4,5-dichloronorlichexanthone (**1-52**),[53] 4,7-dichloronorlichexanthone (**2-23**) and 5,7-dichloronorlichexanthone (**3-26**). The identity of 4,7-dichloronorlichexanthone (**2-23**) was confirmed by direct comparison with synthetic material, this being the first reported occurrence of a natural norlichexanthone derivative with the 4,7-dichloro substitution pattern. The complement of dichloronorlichexanthone derivatives present in this species implies that there is some

selectivity shown by the enzyme responsible for nuclear chlorination as no 2-chloro derivatives were detected, but little discrimination between the 4, 5 and 7 positions *en route* to the predominant 4,5,7-trichloro derivatives present.

Subsequently an undescribed Australian *Buellia* species was surveyed, although it had been established previously that isoarthothelin **(1-29)** was the major constituent present.[44] The precise structure of isoarthothelin was determined in this work (see section **3.b.**). Comparative h.p.l.c. and t.l.c. of the total extract of this species confirmed the presence of thiophanic acid **(1-30)**, isoarthothelin **(1-29)** (major), arthothelin **(1-28)**, 2,5-dichloronorlichexanthone **(3-45)**,[79] 2,7-dichloronorlichexanthone **(2-22)**, and 5,7-dichloronorlichexanthone **(3-26)** (**Figure 3-4**). In this case it is again possible to propose a rational biosynthetic route which would give rise to the combination of dichloro- and trichloronorlichexanthone present (i.e. selective chlorination in the 2, 5 and 7- positions).

The synthetic sample of 2,4,7-trichloronorlichexanthone **(2-26)** proved to be identical (t.l.c., h.p.l.c., m.s.) with a minor metabolite present in the lichens *Lecanora sulphurata* (Ach.) Nyl. and *L. flavo-pallescens* Nyl. The isomeric 2,5,7-trichloronorlichexanthone (isoarthothelin) **(1-29)** was previously reported to be the major trichloroxanthone present in these two species,[108,119,120] but the present work shows this not to be so (see section **3.b.**). Comparative chromatography (t.l.c., h.p.l.c.) confirmed the presence of significant quantities of arthothelin **(1-28)** and 2,4,7-trichloronorlichexanthone **(2-26)** in *L. sulphurata* together with traces of isoarthothelin **(1-29)** (**Table 3-1**). Thiophanic acid **(1-30)** was the major constituent of *L. sulphurata*. In addition to **(1-30)**, the New Zealand species *L. flavo-pallescens* was shown to contain significant quantities of 2,4,7-trichloronorlichexanthone **(2-26)**,

Figure 3-4. H.p.l.c. Traces of Total Lichen Extract



Lichens tested:

A, *Lecanora broccha* (P. W. James 2221 in BM);

B, *Lecidella asema* (W. Brunnbauer 5772 in BSB);

C, *Lecidella subalpicida* (J. A. Elix 593 in ANUC);

D, *Buellia* sp. (J. A. Elix 4569b in ANUC).

Index to h.p.l.c. peaks:

(1) arthothelin (**1-28**); (2) 2,5-dichloronorlichexanthone (**3-45**); (3) 2,7-dichloronorlichexanthone (**2-22**); (4) 4,5-dichloronorlichexanthone (**1-52**); (5) 4,7-dichloronorlichexanthone (**2-23**); (6) 5,7-dichloronorlichexanthone (**3-26**); (7) 5,7-dichloro-3-*O*-methylnorlichexanthone (**3-25**); (8) isoarthothelin (**1-29**); (9) thiophanic acid (**1-30**); (10) 2,5,7-trichloro-3-*O*-methylnorlichexanthone (**3-24**); (11) 4,5,7-trichloronorlichexanthone (asemone) (**3-44**); (12) 4,5,7-trichloro-3-*O*-methylnorlichexanthone (3-*O* -methylasemone) (**2-29**); (13) vicanicin (**3-42**); (14) *O*-methylvicanicin (**3-43**); (15) unknowns.

arthothelin (**1-28**) and 4,5-dichloronorlichexanthone (**1-52**), but no trace of isoarthothelin (**1-29**). Resolution of 2,4,7-trichloronorlichexanthone (**2-26**) and isoarthothelin (**1-29**) by thin-layer chromatography (t.l.c.) was very difficult and this may account for the previous confusion of these two compounds.[108,119,120] However these isomers are readily resolved by high-performance liquid chromatography (h.p.l.c.) as shown in **Table 3-1**. This is the first reported natural occurrence of 2,4,7-trichloronorlichexanthone (**2-26**).

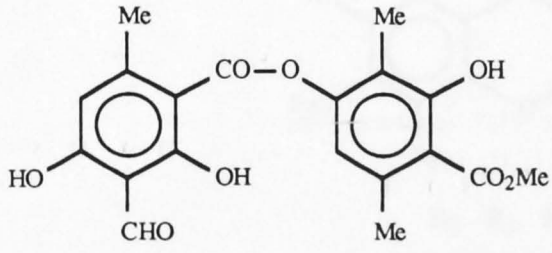
Table 3-1. Resolution of Isomers by H.p.l.c.

Compound	Approximate composition (%)			H.p.l.c.
	Micarea austoternaria	*Lecanora sulphurata*	*Lecanora flavo-pallescens*	R_t (min)
4,5,7-Trichloronorlichexanthone (**3-44**)	9.1	—	—	6.95
2,4,7-Trichloronorlichexanthone (**2-26**)	—	1.3	4.3	6.90
Isoarthothelin (**1-29**)	—	0.8	—	6.60
Arthothelin (**1-28**)	9.3	3.4	25.0	6.13
Thiophanic acid (**1-30**)	70.2	83.3	60.9	8.34
4,5-Dichloronorlichexanthone (**1-52**)	2.6	—	6.1	5.20
Atranorin	—	9.5	—	7.42
Unknowns	8.6	1.7	3.7	—

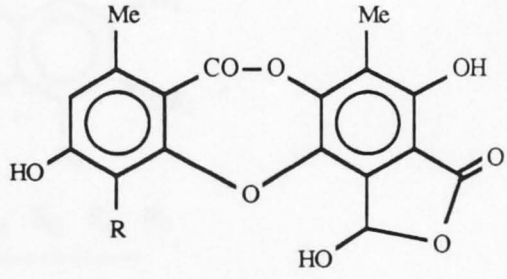
Chapter 4. Two New Xanthones From An Australian *Dimelaena* Lichen

4.a. Background

A recent study of the crude extract of an unnamed *Dimelaena* species from the Kimberley region of Western Australia indicated the presence of seven phenolic compounds.[28] These included the depside atranorin (**4-1**), the depsidones norstictic acid (**4-2**) and connorstictic acid (**4-3**), and the xanthones 6-*O*-methylarthothelin (**4-4**), 2,4,5-trichlorolichexanthone (**4-5**) and 1,3,6-tri-*O*-methylarthothelin (**4-6**). But at that time the nature of a minor xanthone fraction remained to be determined.

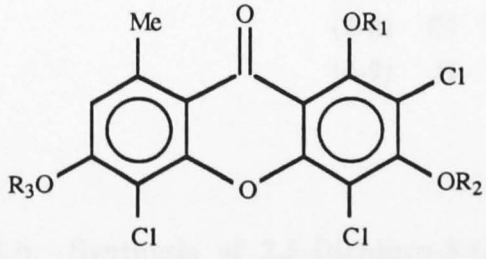


(4-1)



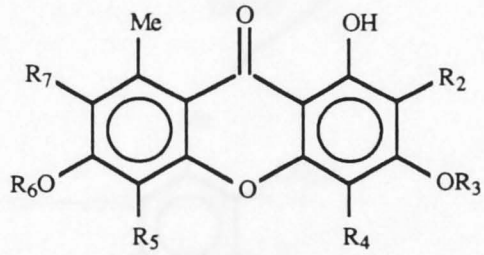
(4-2) R = CHO

(4-3) R = CH_2OH



	R_1	R_2	R_3
(4-4)	H	H	Me
(4-5)	H	Me	Me
(4-6)	Me	Me	Me

Subsequent high performance liquid chromatography (h.p.l.c.) and mass spectrometry (m.s.) has now confirmed that this fraction contained three isomeric dichloroxanthones. Thiophaninic acid (**1-53**) was readily confirmed to be present in this particular species by comparison with authentic material, but the structures of the other two unknown xanthones were not elucidated until total synthesis of three isomeric xanthones, 2,5-dichloro-3-*O*-methylnorlichexanthone (**4-7**), 2,5-dichloro-6-*O*-methylnorlichexanthone (**4-8**) and 4,5-dichloro-6-*O*-methylnorlichexanthone (**4-9**), had been completed. Direct comparison between the natural and synthetic materials then established that the xanthones occurring in this *Dimelaena* species were 2,5-dichloro-6-*O*-methylnorlichexanthone (**4-8**) and 4,5-dichloro-6-*O*-methylnorlichexanthone (**4-9**).

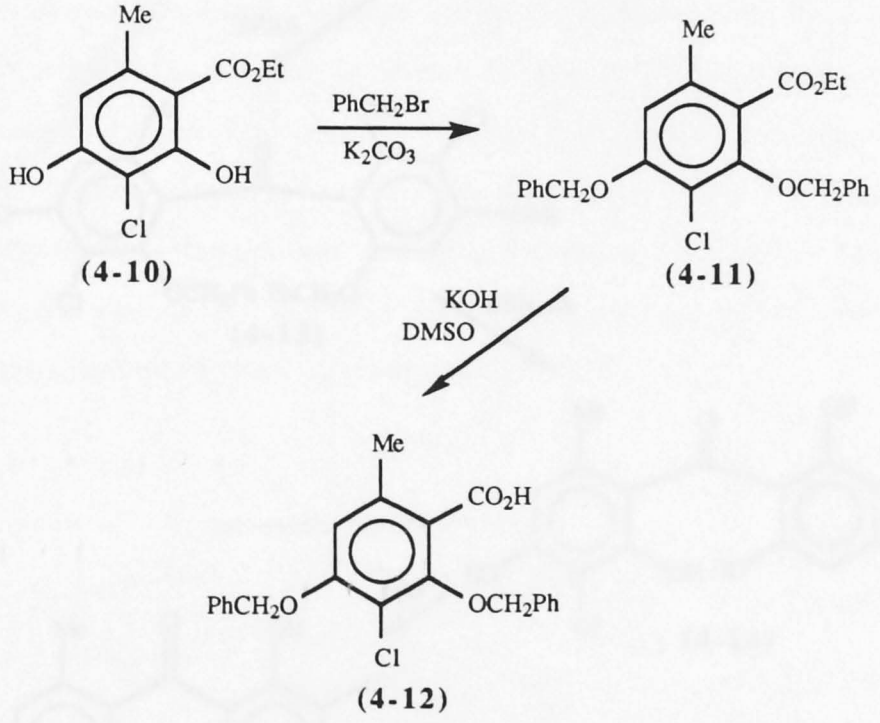


	R_2	R_3	R_4	R_5	R_6	R_7
(1-53)	Cl	H	Cl	H	Me	H
(4-7)	Cl	Me	H	Cl	H	H
(4-8)	Cl	H	H	Cl	Me	H
(4-9)	H	H	Cl	Cl	Me	H

4.b. Synthesis of 2,5-Dichloro-3-*O*-methylnorlichexanthone

The xanthone 2,5-dichloro-3-*O*-methylnorlichexanthone (**4-7**) has been prepared previously by Sundholm,[119] but was resynthesized (**Scheme 4-2**) in order to make direct chromatographic comparison (t.l.c., h.p.l.c.) possible.

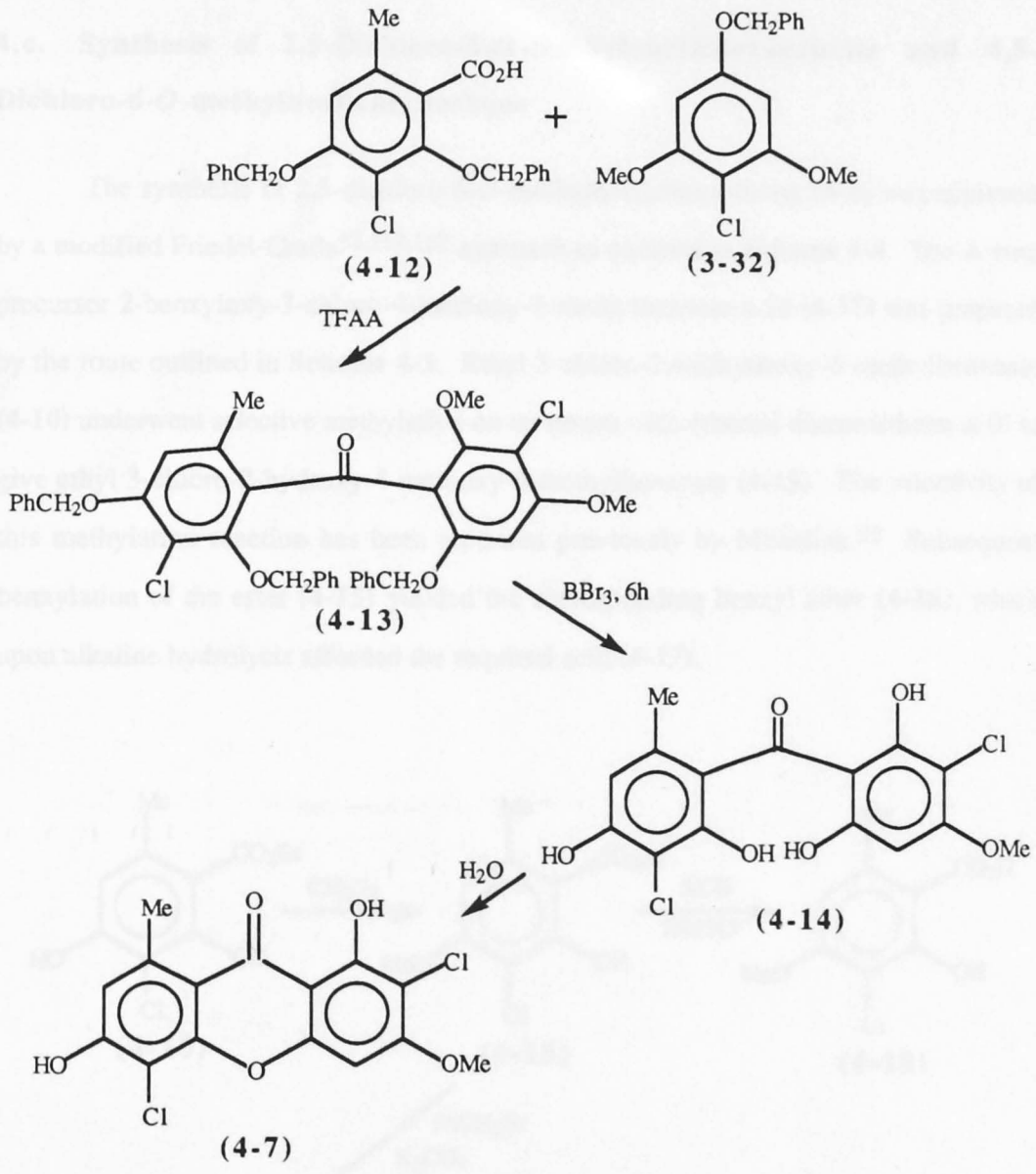
The key mononuclear precursor 2,4-dibenzyloxy-3-chloro-6-methylbenzoic acid (**4-12**) was prepared from ethyl 3-chloro-2,4-dihydroxy-6-methylbenzoate (**4-10**) by benzylation and hydrolysis (**Scheme 4-1**).[39]



(4-10) **(4-11)** **(4-12)**

Scheme 4-1

Condensation of the acid (**4-12**) and 5-benzyloxy-2-chloro-1,3-dimethoxybenzene (**3-32**) in the presence of trifluoroacetic anhydride yielded the corresponding benzophenone (**4-13**). This benzophenone (**4-13**) underwent debenzylation and selective demethylation by a brief treatment with boron tribromide to yield the tetrahydroxybenzophenone (**4-14**), which was then cyclised in boiling water to give the required xanthone, 2,5-dichloro-3-*O*-methylnorlichexanthone (**4-7**).

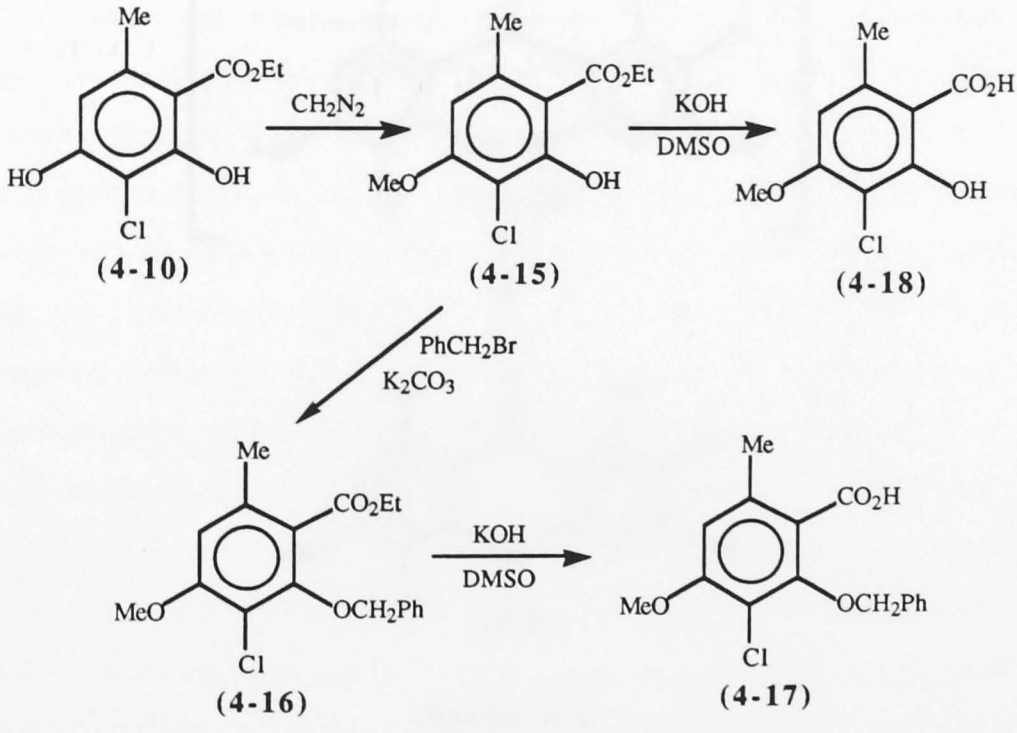


Scheme 4-2

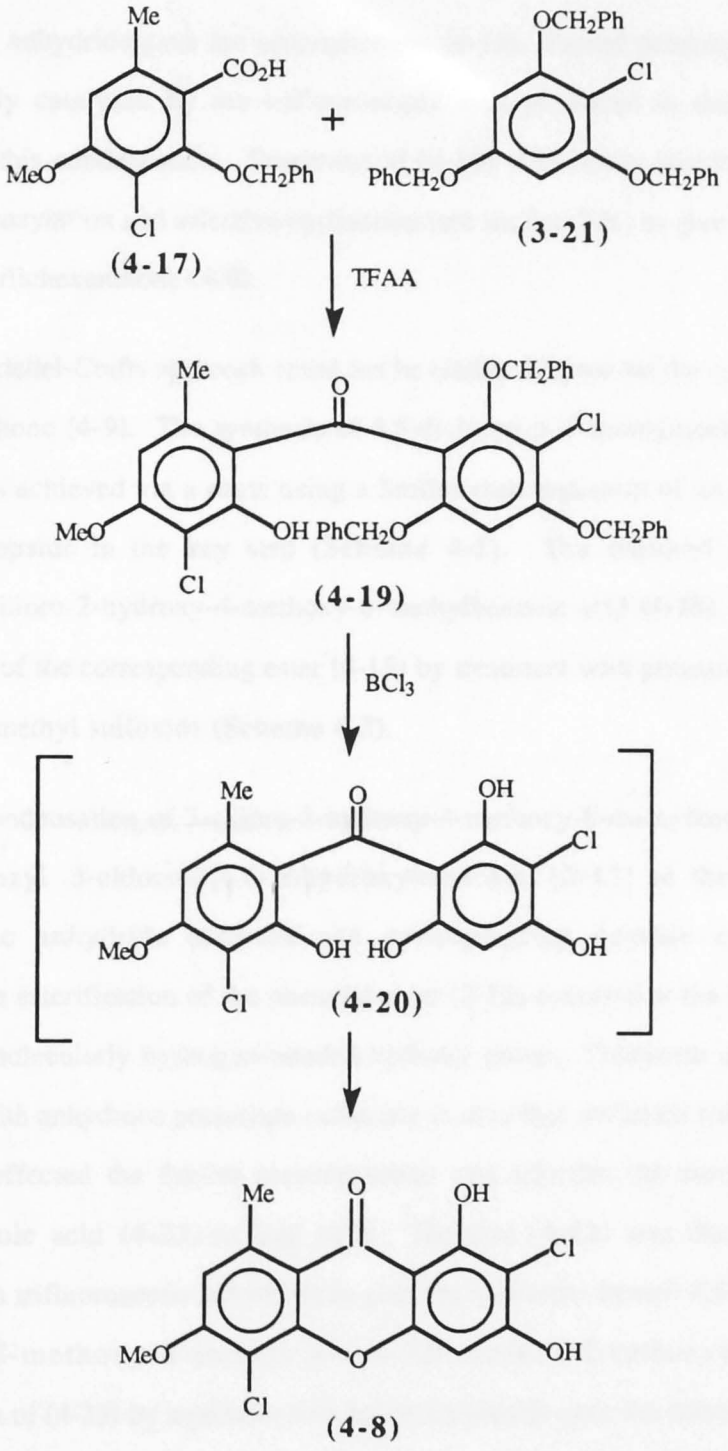
Chromatographic comparison (t.l.c., h.p.l.c.) between the synthetic xanthone (**4-7**) and the natural unknowns established that there was no trace of the xanthone 2,5-dichloro-3-*O*-methylnorlichexanthone (**4-7**) present in the *Dimelaena* lichen.

4.c. Synthesis of 2,5-Dichloro-6-*O*-methylnorlichexanthone and 4,5-Dichloro-6-*O*-methylnorlichexanthone

The synthesis of 2,5-dichloro-6-*O*-methylnorlichexanthone (**4-8**) was achieved by a modified Friedel-Crafts[53,119,122] approach as outlined in **Scheme 4-4**. The A-ring precursor 2-benzyloxy-3-chloro-4-methoxy-6-methylbenzoic acid (**4-17**) was prepared by the route outlined in **Scheme 4-3**. Ethyl 3-chloro-2,4-dihydroxy-6-methylbenzoate (**4-10**) underwent selective methylation on treatment with ethereal diazomethane at 0° to give ethyl 3-chloro-2-hydroxy-4-methoxy-6-methylbenzoate (**4-15**). The selectivity of this methylation reaction has been recorded previously by Musidlak.[92] Subsequent benzylation of the ester (**4-15**) yielded the corresponding benzyl ether (**4-16**), which upon alkaline hydrolysis afforded the required acid (**4-17**).



Scheme 4-3



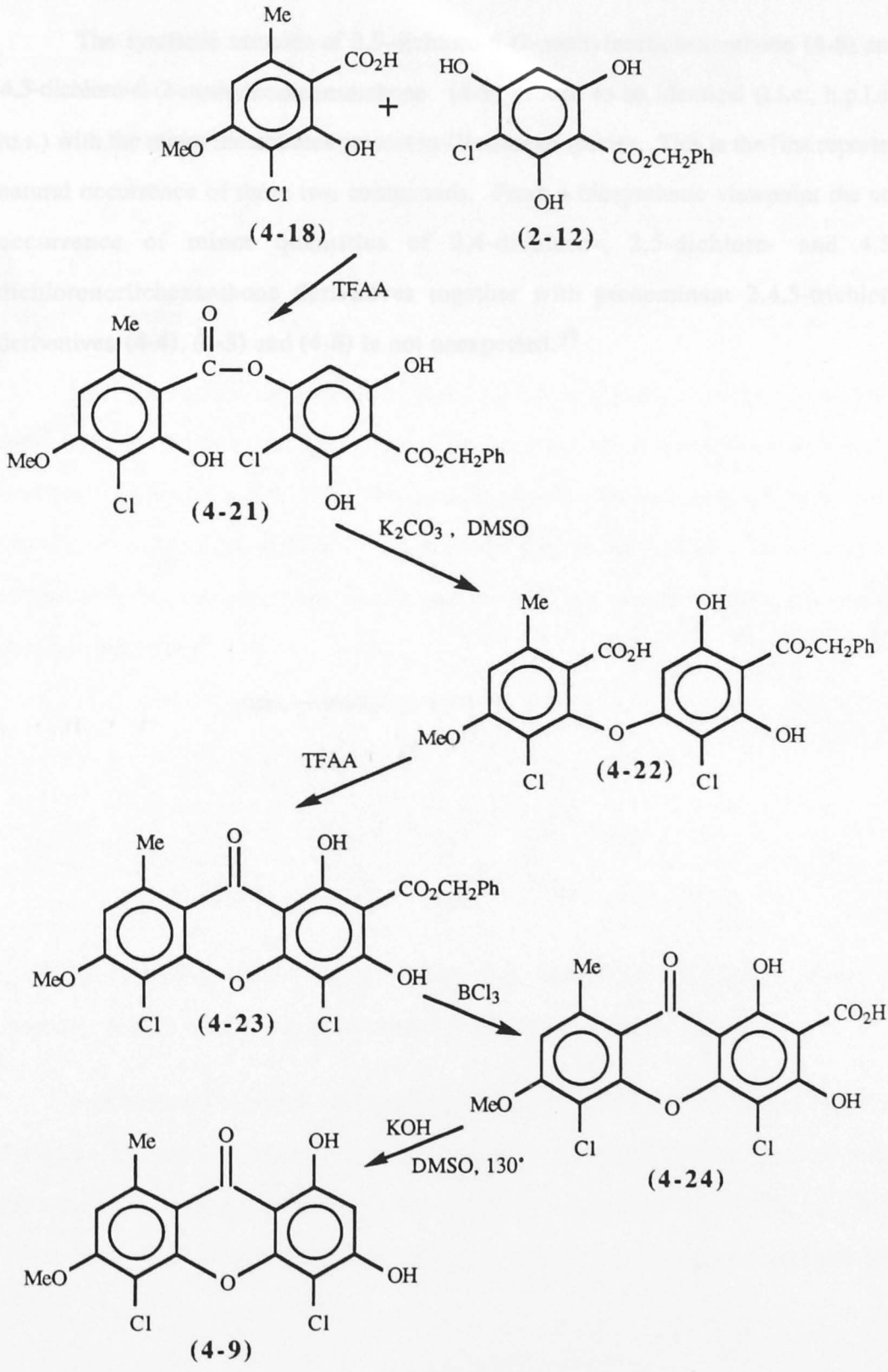
Scheme 4-4

Subsequent condensation of 2-benzyloxy-3-chloro-4-methoxy-6-methylbenzoic acid **(4-17)** and 1,3,5-tribenzyloxy-2-chlorobenzene **(3-21)** in the presence of

trifluoroacetic anhydride gave the benzophenone (**4-19**). Partial debenzylation which was apparently catalysed by the trifluoroacetic acid produced in the initial step, accompanied this condensation. Treatment of (**4-19**) with boron trichloride effected complete debenzylation and selective cyclisation (see section **3.b.**) to give 2,5-dichloro-6-*O*-methylnorlichexanthone (**4-8**).

This Friedel-Crafts approach could not be readily adapted for the synthesis of the isomeric xanthone (**4-9**). The synthesis of 4,5-dichloro-6-*O*-methylnorlichexanthone (**4-9**) was thus achieved via a route using a Smiles rearrangement of an appropriately substituted depside in the key step (**Scheme 4-5**). The required mononuclear precursor, 3-chloro-2-hydroxy-4-methoxy-6-methylbenzoic acid (**4-18**), was prepared by hydrolysis of the corresponding ester (**4-15**) by treatment with potassium hydroxide in aqueous dimethyl sulfoxide (**Scheme 4-3**).

The condensation of 3-chloro-2-hydroxy-4-methoxy-6-methylbenzoic acid (**4-18**) and benzyl 3-chloro-2,4,6-trihydroxybenzoate (**2-12**) in the presence of trifluoroacetic anhydride afforded the corresponding depside ester (**4-21**). Regioselective esterification of the phenolic ester (**2-12**) occurred at the less hindered, weakly intramolecularly hydrogen-bonded hydroxy group. Treatment of the depside ester (**4-21**) with anhydrous potassium carbonate in dimethyl sulfoxide solution at room temperature effected the Smiles rearrangement and afforded the corresponding 2-phenoxybenzoic acid (**4-22**) in high yield. The acid (**4-22**) was then cyclised by treatment with trifluoroacetic anhydride to give the xanthone, benzyl 4,5-dichloro-1,3-dihydroxy-6-methoxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylate (**4-23**). Debenzylation of (**4-23**) by treatment with boron trichloride gave the corresponding acid (**4-24**). When the acid (**4-24**) was heated with potassium hydroxide in aqueous dimethyl sulfoxide solution at 120-140°, decarboxylation occurred to afford 4,5-dichloro-6-*O*-methylnorlichexanthone (**4-9**).


Me
CO2H
MeO
OH
Cl
(4-18)
+
HO
OH
Cl
CO2CH2Ph
OH
(2-12)
TFAA
O
C—O
(4-21)
K2CO3 , DMSO
(4-22)
TFAA
(4-23)
BCl3
(4-24)
KOH
DMSO, 130°
(4-9)

Scheme 4-5

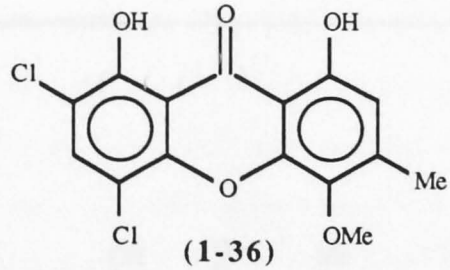
The synthetic samples of 2,5-dichloro-6-*O*-methylnorlichexanthone (**4-8**) and 4,5-dichloro-6-*O*-methylnorlichexanthone (**4-9**) proved to be identical (t.l.c., h.p.l.c., m.s.) with the minor metabolites present in *Dimelaena* species. This is the first reported natural occurrence of these two compounds. From a biosynthetic viewpoint the co-occurrence of minor quantities of 2,4-dichloro-, 2,5-dichloro- and 4,5-dichloronorlichexanthone derivatives together with predominant 2,4,5-trichloro derivatives (**4-4**), (**4-5**) and (**4-6**) is not unexpected.[37]

Chapter 5. Structure And Synthesis Of Thiomelin Derivatives

5.a. Background

In 1984 Leuckert and Mayrhofer[84] isolated four xanthone pigments, thiomelin, TH1, TH2 and TH3, from the lichens *Rinodina thiomela* (Nyl.) Müll. Arg. and *Rinodina lepida* (Nyl.) Müll. Arg., but the structures of these compounds could not be determined.

Elix, Gaul et al.[41] undertook the subsequent reisolation and identification of the above mentioned pigments. Their large scale extraction of an Australian collection of *Rinodina thiomela* gave three of the previously reported pigments namely thiomelin, TH1 and TH2 as well as three additional ones, but they failed to isolate TH3. The structure of thiomelin **(1-36)** was ultimately determined by an X-ray crystal structure analysis of thiomelin diacetate.[41]

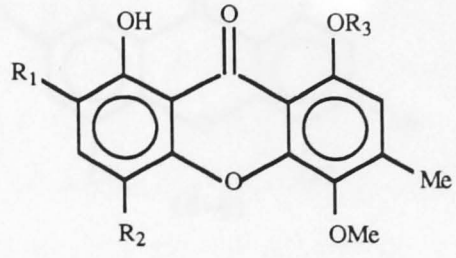


(1-36)

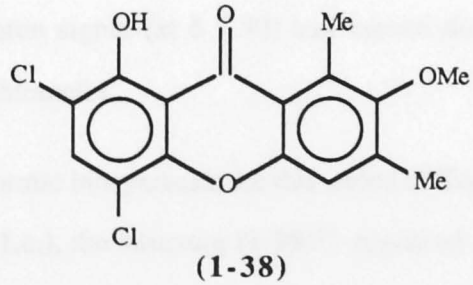
Elix and Portelli[34,97] have subsequently completed the total synthesis of thiomelin, further confirming the structure **(1-36)** for this compound.

Spectroscopic studies confirmed that all of the five co-occurring metabolites were related to thiomelin **(1-36)** and from a comparative study of the ^1H n.m.r. and mass spectral data four of these xanthones were assigned structures **(1-37)** and **(5-1)**–**(5-3)** **(Table 5-1)**, while the remaining pigment, TH2, was tentatively assigned structure **(1-38)**.

Table 5-1 Assigned Structures of Thiomelin Derivatives

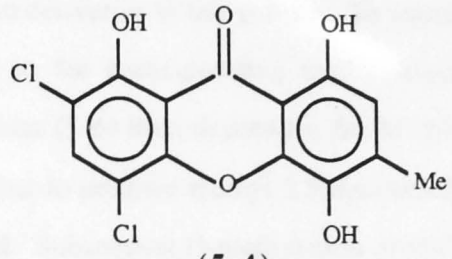


	R_1	R_2	R_3	Compound
(5-1)	Cl	Cl	Me	8-*O*-Methylthiomelin
(1-37)	Cl	H	H	4-Dechlorothiomelin (TH1)
(5-2)	Cl	H	Me	4-Dechloro-8-*O*-methylthiomelin
(5-3)	H	Cl	Me	2-Dechloro-8-*O*-methylthiomelin



(1-38)

Further, Leuckert and Mayrhofer[84] deduced from the mass spectral data that the xanthone TH3 was northiomelin (i.e. **5-4**).



(5-4)

The unambiguous synthesis of the xanthones **(1-37)**, **(1-38)** and **(5-2)**–**(5-4)** was undertaken in order to confirm the assigned structures.

5.b. Synthesis of 2,4-Dichloro-1-hydroxy-7-methoxy-6,8-dimethyl-9*H*-xanthen-9-one (TH2)

Elix, Gaul et al.[41] deduced the structure of TH2 **(1-38)** from an analysis of the spectroscopic properties of this compound as well as its presumed biosynthesis (see section **1.e.**). The ^{1}H n.m.r. spectrum of **(1-38)** indicated that ring A was identically substituted with that of thiomelin **(1-36)**. However ring B appeared to differ from thiomelin by the substitution of a hydroxy group with a *C*-methyl group. In addition, the remaining aromatic proton signal (at δ 7.30) had moved downfield by 0.63 ppm in comparison with H7 of thiomelin.

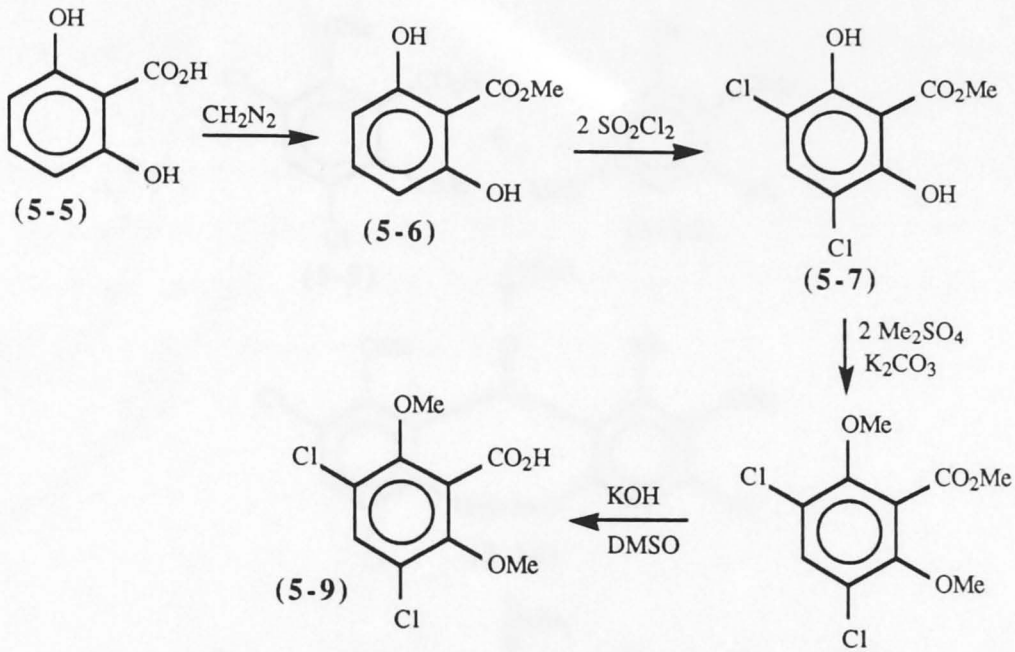
Considering a normal biosynthesis for this series of 'fungal type' xanthones (see **Scheme 1-4** in section **1.e.**), the structure **(1-38)**[41] appeared reasonable.

Thus an unambiguous synthesis of the xanthone **(1-38)** was carried out as outlined in **Scheme 5-3**, while the preparation of the two key precursors is illustrated in **Schemes 5-1** and **5-2**. 3,5-Dichloro-2,6-dimethoxybenzoic acid **(5-9)** was prepared as described previously.[34,97] Direct chlorination of 2,6-dihydroxybenzoic acid **(5-5)** using sulfuryl chloride in ether was unsatisfactory due to the low solubility of both the

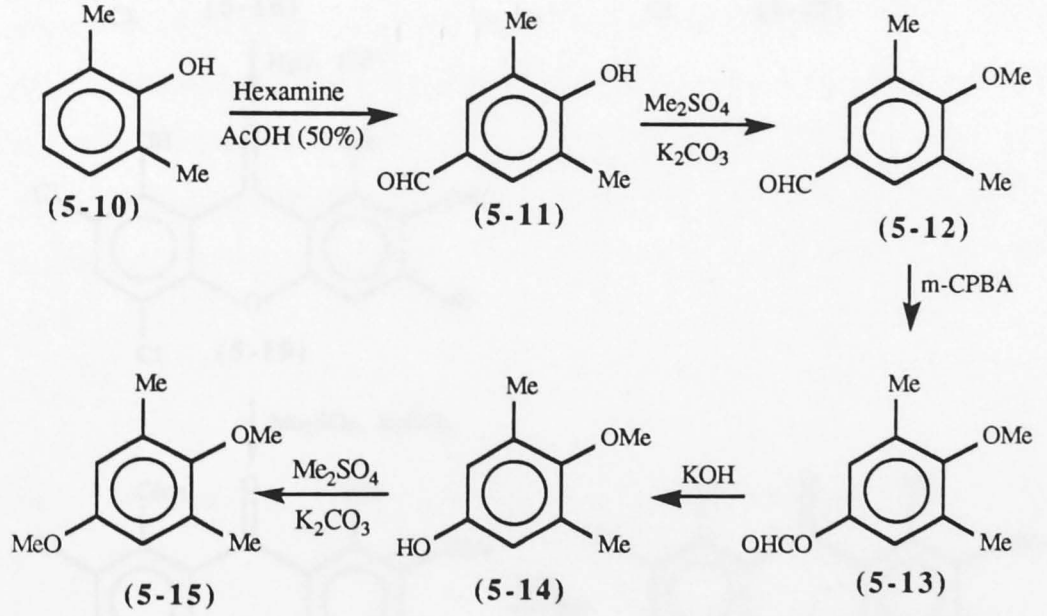
acid and its monochloro derivative in this solvent. To circumvent this problem, the acid (**5-5**) was converted to the corresponding methyl ester (**5-6**) by treatment with diazomethane. The ester (**5-6**) then underwent facile chlorination on treatment with sulfuryl chloride in ether to produce methyl 3,5-dichloro-2,6-dihydroxybenzoate (**5-7**) in relatively high yield. Subsequent *O*-methylation of (**5-7**) was effected by treatment with dimethyl sulfate and anhydrous potassium carbonate to give methyl 3,5-dichloro-2,6-dimethoxybenzoate (**5-8**), and alkaline hydrolysis of this compound afforded the required 3,5-dichloro-2,6-dimethoxybenzoic acid (**5-9**).

The preparation of the other precursor, 1,4-dimethoxy-2,6-dimethylbenzene (**5-15**) was achieved using the Duff reaction[1,26] in the key step. Treatment of 2,6-dimethylphenol (**5-10**) with hexamethylenetetramine (hexamine) in aqueous acetic acid gave an intermediate Schiff base which on hydrolysis with hydrochloric acid yielded 4-hydroxy-3,5-dimethylbenzaldehyde (**5-11**). Subsequent methylation of this phenol (dimethyl sulfate, potassium carbonate) followed by Baeyer-Villiger oxidation of the 4-methoxy-3,5-dimethylbenzaldehyde (**5-12**) with *m*-chloroperbenzoic acid (m-CPBA), afforded the intermediate 4-methoxy-3,5-dimethylphenyl formate (**5-13**). Mild alkaline hydrolysis of the formate (**5-13**) then gave the phenol, 4-methoxy-3,5-dimethylphenol (**5-14**), while methylation of this compound under the usual conditions afforded the required ether, 1,4-dimethoxy-2,6-dimethylbenzene (**5-15**).

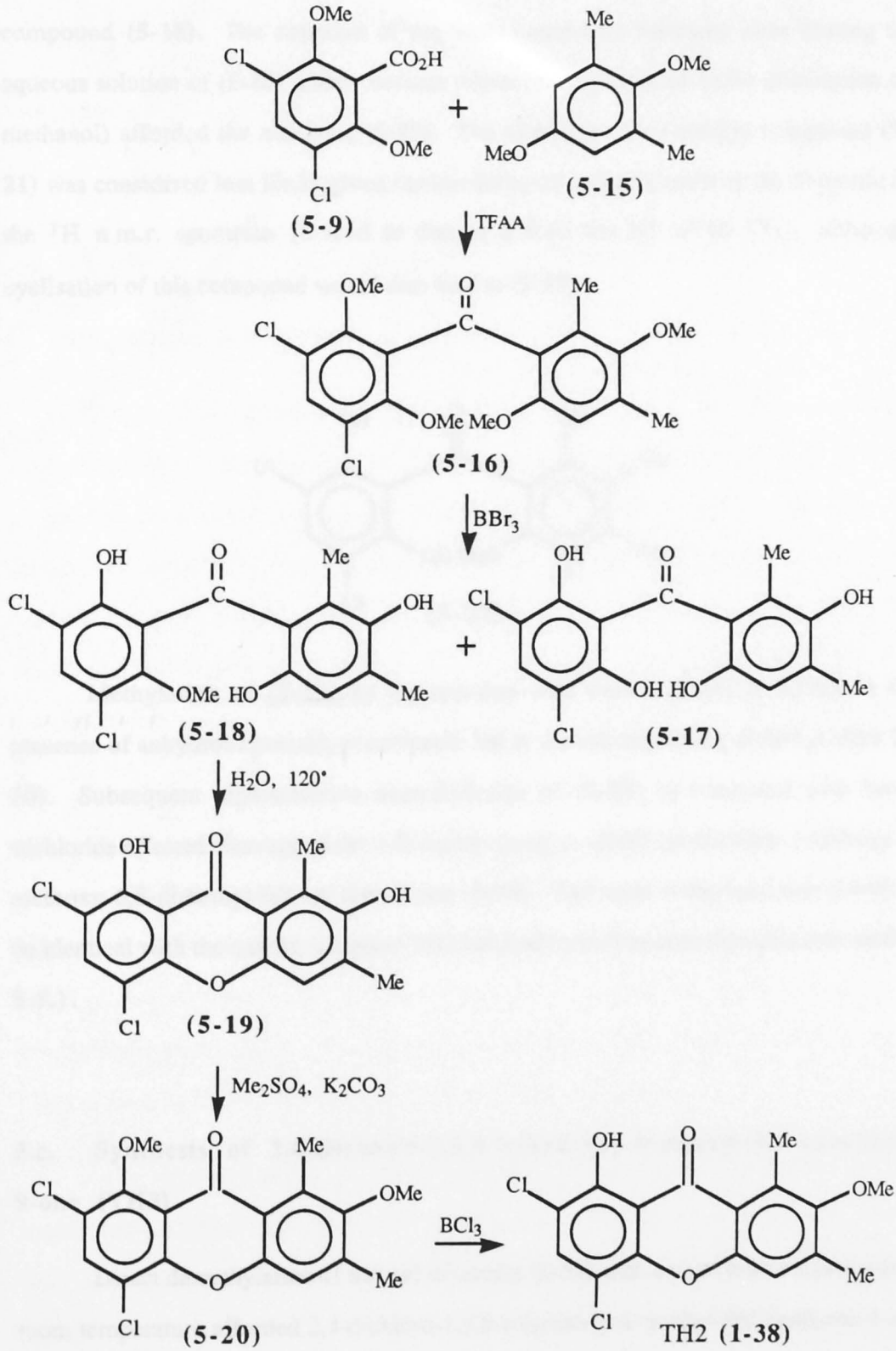
The synthesis of the xanthones (**1-38**) and (**5-19**) was achieved by using the Friedel-Crafts approach developed by Sundholm[120,122] and by Fitzpatrick and Sargent.[53] Thus acylation of 1,4-dimethoxy-2,6-dimethylbenzene (**5-15**) by 3,5-dichloro-2,6-dimethoxybenzoic acid (**5-9**) in the presence of trifluoroacetic anhydride afforded the benzophenone, 3,5-dichloro-2,3',6,6'-tetramethoxy-2',4'-dimethylbenzophenone (**5-16**) (**Scheme 5-3**). Partial demethylation of (**5-16**) by brief treatment with boron tribromide afforded two products, 3,5-dichloro-2,3',6,6'-tetrahydroxy-2',4'-dimethylbenzophenone (**5-17**) and the corresponding 6-*O*-methyl



Scheme 5-1

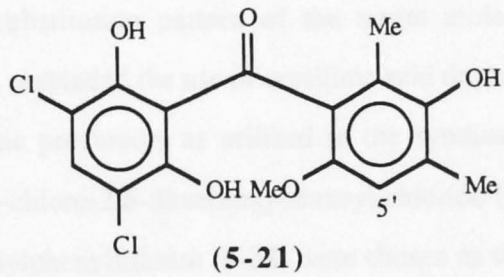


Scheme 5-2


OMe
Cl
CO2H
OMe
Cl
(5-9)
+
Me
OMe
MeO
Me
(5-15)
TFAA
OMe
O
Me
Cl
C
OMe
OMe MeO
Me
Cl
(5-16)
BBr3
OH
O
Me
Cl
C
OH
OMe HO
Me
Cl
(5-18)
+
OH
O
Me
Cl
C
OH
OH HO
Me
Cl
(5-17)
H2O, 120°
OH
O
Me
Cl
OH
Me
Cl
(5-19)
Me2SO4, K2CO3
OMe
O
Me
Cl
OMe
Me
Cl
(5-20)
BCl3
OH
O
Me
Cl
OMe
Me
Cl
TH2 (1-38)

Scheme 5-3

compound **(5-18)**. The structure of the latter compound followed after heating an aqueous solution of **(5-18)** under pressure whereupon cyclisation (with elimination of methanol) afforded the xanthone **(5-19)**. The alternative 6'-*O*-methyl compound **(5-21)** was considered less likely given the similarity of chemical shift of the 5'-proton in the ^{1}H n.m.r. spectrum [δ 6.65 to that of δ 6.63 for H5' of **(5-17)**], although cyclisation of this compound would also lead to **(5-19)**.



(5-21)

Methylation of **(5-19)** by the reaction with excess dimethyl sulfate in the presence of anhydrous potassium carbonate led to the corresponding dimethyl ether **(5-20)**. Subsequent regioselective demethylation of **(5-20)** by treatment with boron trichloride effected cleavage of the 1-*O*-methyl group to afford 2,4-dichloro-1-hydroxy-7-methoxy-6,8-dimethyl-9*H*-xanthen-9-one **(1-38)**. The latter compound was shown to be identical with the natural xanthone TH2 isolated from *Rinodina thiomela* (see section **5.f.**).

5.c. Synthesis of 2,4-Dichloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthene-9-one (TH3)

Direct demethylation of natural thiomelin **(1-36)** with excess boron tribromide at room temperature afforded 2,4-dichloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthone-9-one (TH3) **(5-4)** directly.

Chromatographic comparisons confirmed that minor amounts of this xanthone were present in the lichen *Rinodina thiomela* (see section **5.f.**).

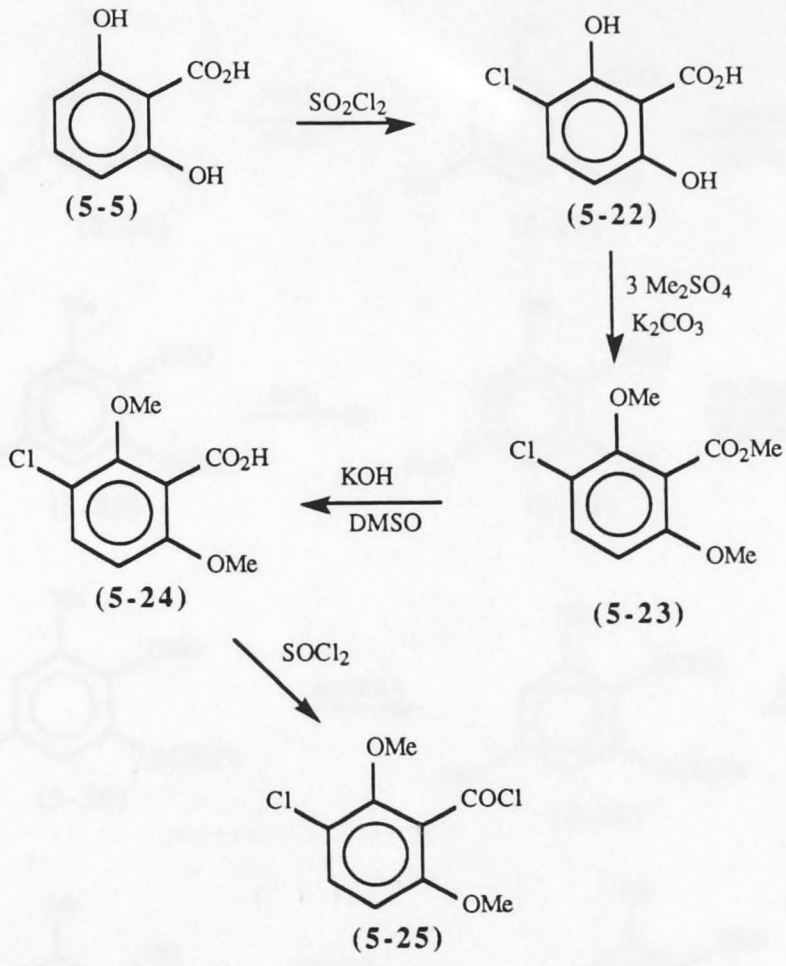
5.d. Synthesis of 2-Dechlorothiomelin and Derivatives

i. Using Organolithium Intermediates

The unusual substitution pattern of the target molecule, 2-dechloro-8-*O*-methylthiomelin **(5-3)**, precluded the use of orsellinic acid or phloroglucinol derivatives as pre-formed aromatic precursors as utilized in the synthesis of norlichexanthone derivatives. Instead 3-chloro-2,6-dimethoxybenzoyl chloride **(5-25)** and 2-benzyloxy-3,6-dimethoxy-4-methylphenyllithium **(5-34)** were chosen as the key precursors for an acylation reaction (**Scheme 5-6**) analogous to that performed by Sundholm[120] and Elix and Portelli.[34] The synthesis of these precursors are outlined in **Schemes 5-4** and **5-5**.

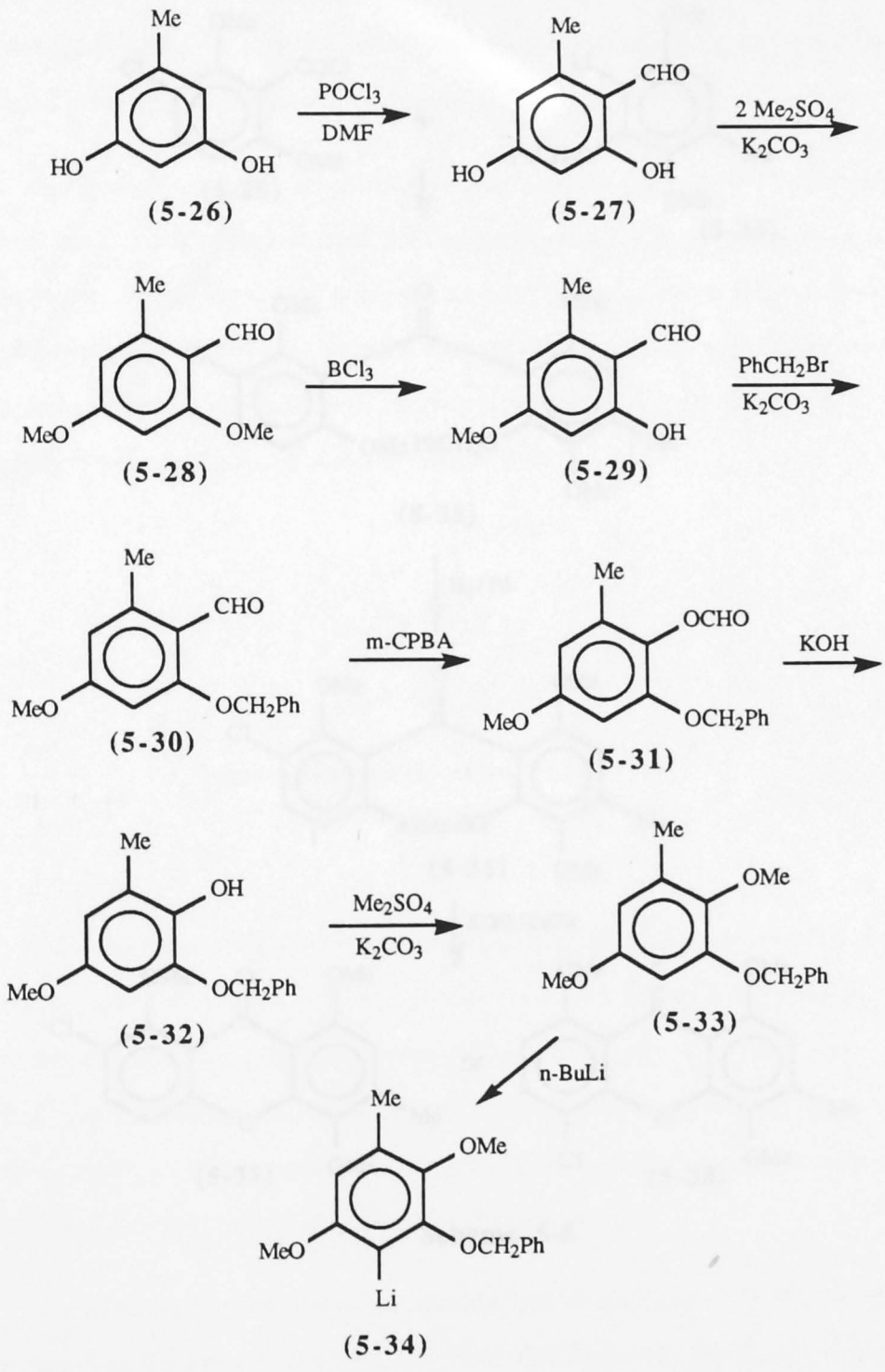
2,6-Dihydroxybenzoic acid **(5-5)** underwent facile chlorination with sulfuryl chloride (1 mole) to give 3-chloro-2,6-dihydroxybenzoic acid **(5-22)**. Treatment of **(5-22)** with dimethyl sulfate in the presence of potassium carbonate gave methyl 3-chloro-2,6-dimethoxybenzoate **(5-23)**, and subsequent alkaline hydrolysis afforded the corresponding acid **(5-24)**. The key intermediate acid chloride **(5-25)** was prepared by treating the acid **(5-24)** with thionyl chloride in refluxing toluene.

The synthesis of the second key intermediate, 2-benzyloxy-3,6-dimethoxy-4-methylphenyllithium **(5-34)**, involved eight steps with orcinol **(5-26)** the starting material (**Scheme 5-5**). Orcinol **(5-26)** underwent Vilsmeier formylation on treatment

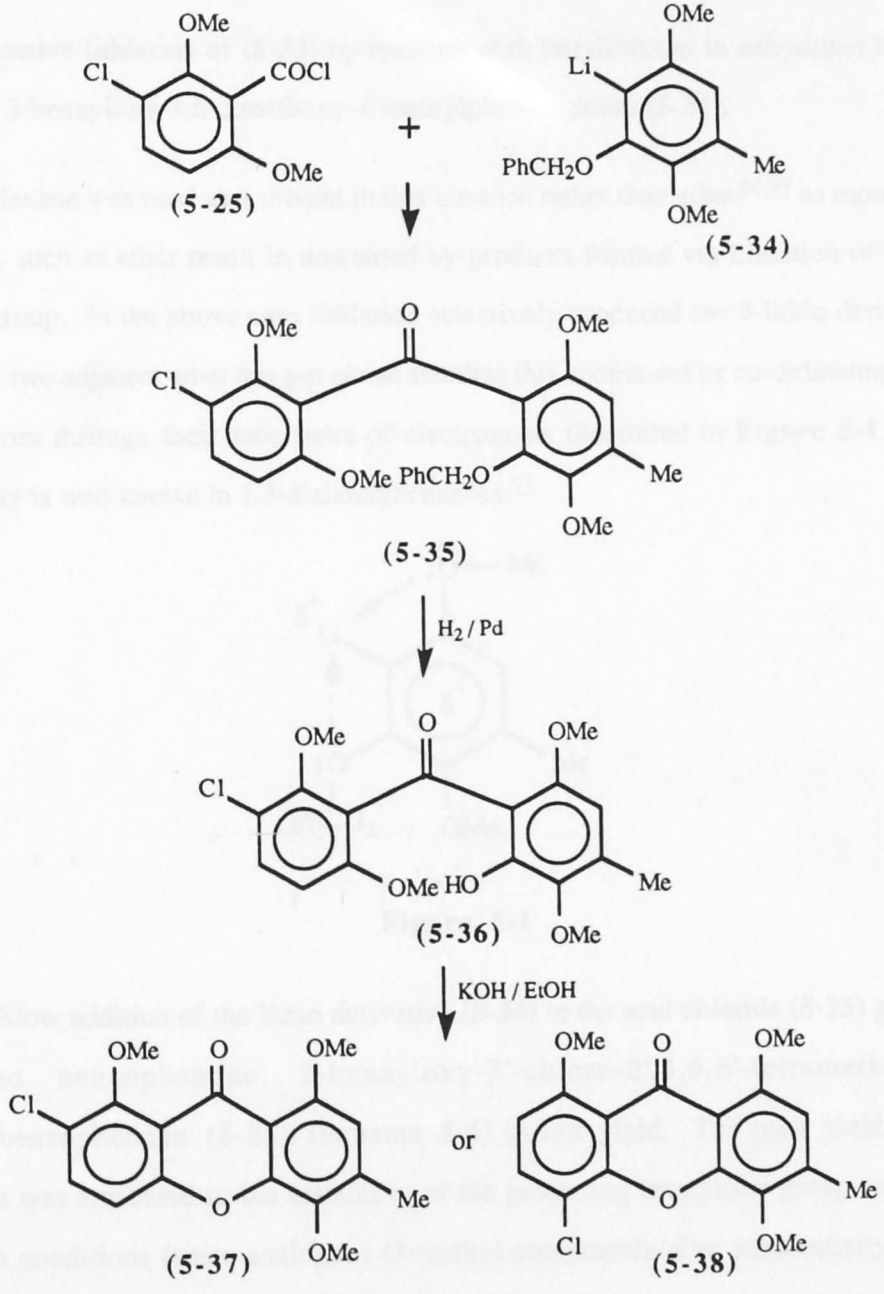


Scheme 5-4

with phosphoryl chloride and *N,N*-dimethylformamide to give 2,4-dihydroxy-6-methylbenzaldehyde (**5-27**). The regioselectivity of this reagent with orcinol and its derivatives has been noted previously.[17,134] Methylation of (**5-27**) with dimethyl sulfate in the presence of potassium carbonate then afforded the dimethyl ether (**5-28**), which on selective demethylation with boron trichloride gave 2-hydroxy-4-methoxy-6-methylbenzaldehyde (**5-29**). Subsequent benzylation of (**5-29**) with benzyl bromide-potassium carbonate yielded the corresponding 2-benzyloxy-4-methoxy-6-methylbenzaldehyde (**5-30**), which was converted to 2-benzyloxy-4-methoxy-6-methyl-


Me
HO
OH
(5-26)
POCl3
DMF
Me
CHO
HO
OH
(5-27)
2 Me2SO4
K2CO3
Me
CHO
MeO
OMe
(5-28)
BCl3
Me
CHO
MeO
OH
(5-29)
PhCH2Br
K2CO3
Me
CHO
MeO
OCH2Ph
(5-30)
m-CPBA
Me
OCHO
MeO
OCH2Ph
(5-31)
KOH
Me
OH
MeO
OCH2Ph
(5-32)
Me2SO4
K2CO3
Me
OMe
MeO
OCH2Ph
(5-33)
n-BuLi
Me
OMe
MeO
OCH2Ph
Li
(5-34)

Scheme 5-5



Scheme 5-6

phenyl formate (**5-31**) by Baeyer-Villiger oxidation with *m*-chloroperbenzoic acid. Mild alkaline hydrolysis of the formate (**5-31**) converted it to the corresponding phenol (**5-32**), which was then methylated to give 3-benzyloxy-2,5-dimethoxytoluene (**5-33**).

Regioselective lithiation of **(5-33)** by reaction with butyllithium in anhydrous hexane afforded 2-benzyloxy-3,6-dimethoxy-4-methylphenyllithium **(5-34)**.

Hexane was used as a solvent in this instance rather than ether[34,97] as more polar solvents, such as ether result in unwanted by-products formed via lithiation of the *O*-benzyl group. In the above case lithiation selectively produced the 4-lithio derivative, since the two adjacent ether oxygen atoms stabilize this compound by co-ordinating to the metal atom through their lone pairs of electrons as illustrated in **Figure 5-1**. Such selectivity is well known in 1,3-dialkoxybenzenes.[35]

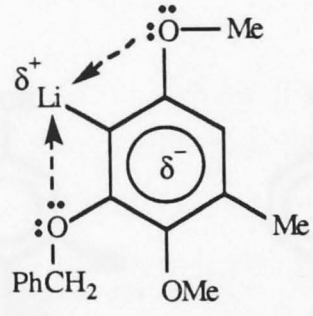


Figure 5-1

Slow addition of the lithio derivative **(5-34)** to the acid chloride **(5-25)** gave the required benzophenone, 2-benzyloxy-3'-chloro-2',3,6,6'-tetramethoxy-4-methylbenzophenone **(5-35)**, (**Scheme 5-6**) in low yield. The poor yield in this reaction was attributed to the instability of the protecting benzyloxy group under the reaction conditions (since analogous *O*-methyl compounds give substantially higher yields)[34] and the steric crowding of the two reaction centres.

Catalytic hydrogenolysis of the intermediate benzophenone **(5-35)** afforded the corresponding hydroxy compound, 3'-chloro-2-hydroxy-2',3,6,6'-tetramethoxy-4-methylbenzophenone **(5-36)**. It was anticipated that base catalysed cyclisation of this benzophenone **(5-36)** would lead to a mixture of the isomeric xanthones **(5-37)** and **(5-38)**, but only one isomer was obtained. Subsequent demethylation of the latter

xanthone with boron trichloride gave rise to two monodemethylated derivatives in a ratio of 2:1. These two isomers were designated **Prod-1** and **Prod-2** (with four alternative structures possible as illustrated in **Figure 5-2**) and their structures were elucidated later (see **iii.**).

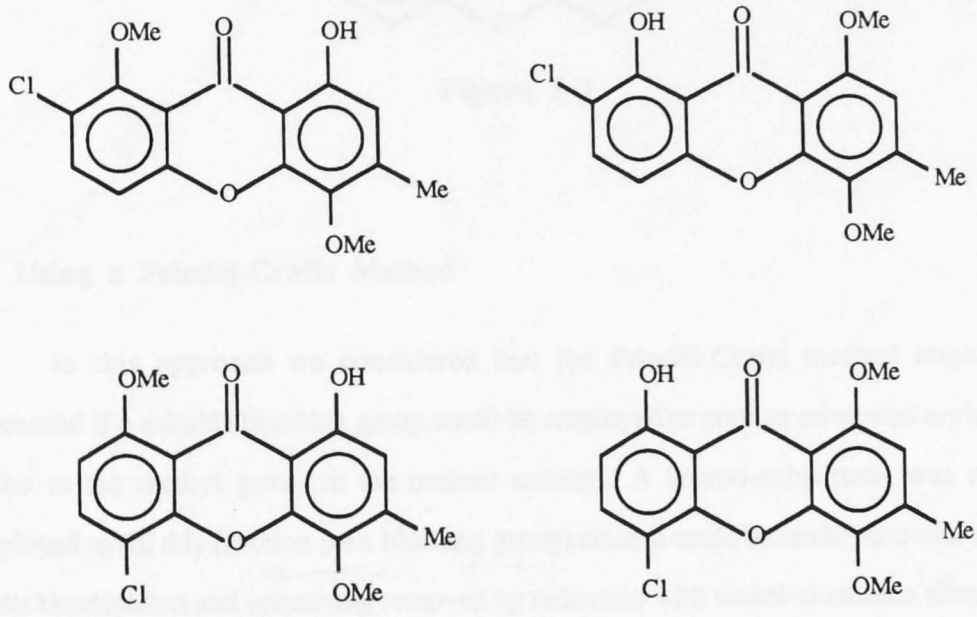


Figure 5-2

The observation that boron trichloride only effects cleavage of one of the methoxy groups oriented *ortho* to the adjacent carbonyl group has been reported previously by Dean et al.[23] and Portelli,[97] but there has not been a satisfatory explanation for this phenomenon. It is thought here that this could be attributed to difficulty in the formation of the second boron complex involving the same carbonyl oxygen atom (**Figure 5-3**).

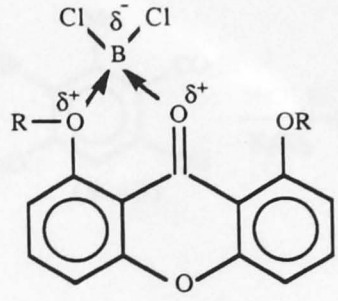
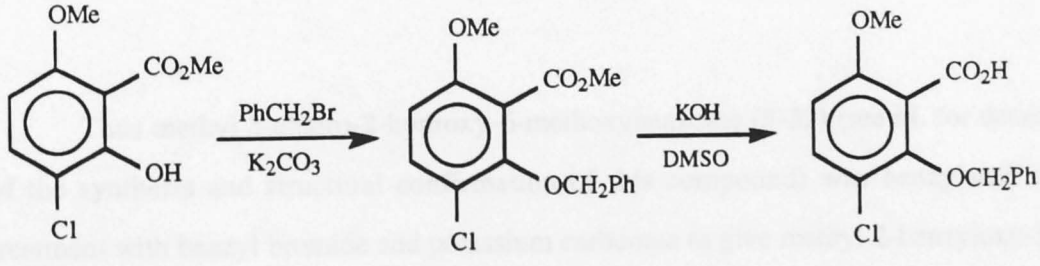


Figure 5-3

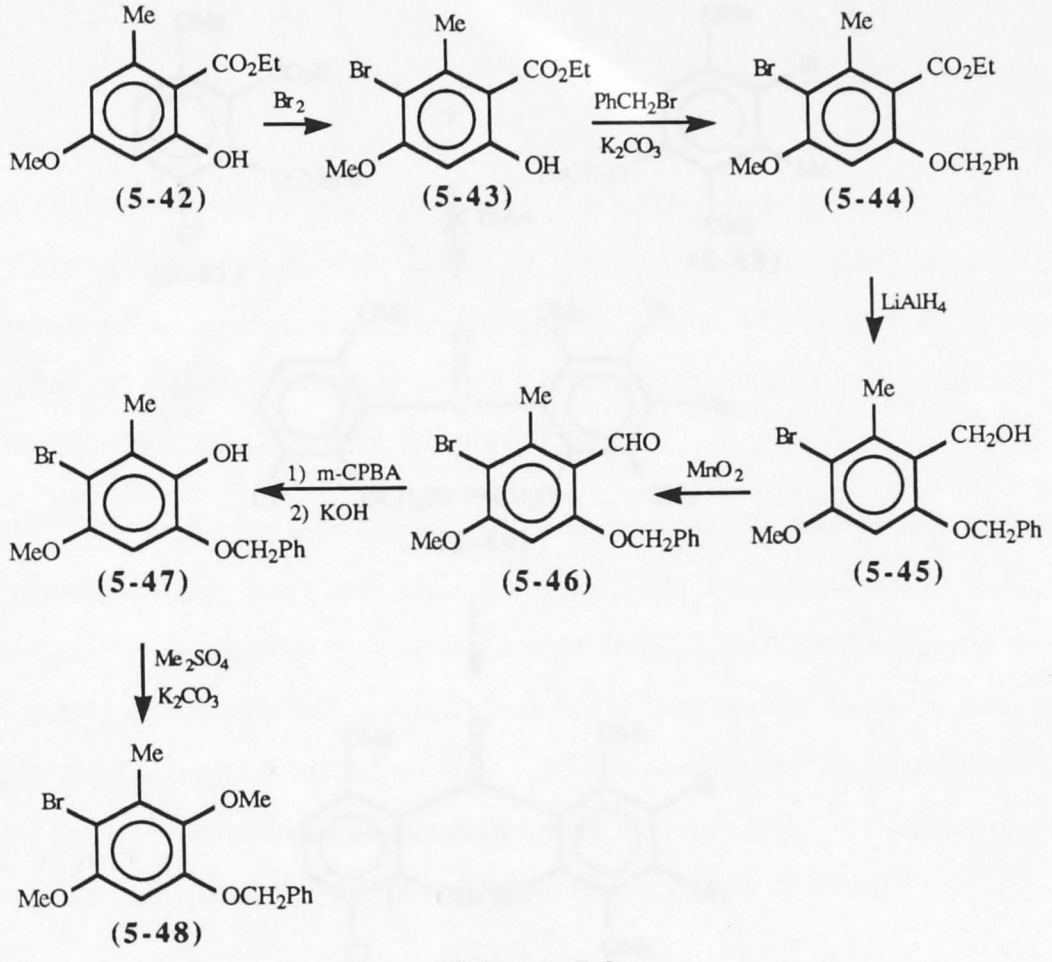
ii. Using a Friedel-Crafts Method

In this approach we considered that the Friedel-Crafts method might be successful if a suitable blocking group could be employed to prevent unwanted acylation *ortho* to the methyl group in the orcinol moiety. A bromo-substituent was to be employed to fill this function (as a blocking group) since it could be readily introduced by direct bromination and selectively removed by reduction with nickel-aluminum alloy and aqueous base. The proposed route to the required xanthone is outlined in **Scheme 5-9**, while the synthetic routes to the key precursors are depicted in **Schemes 5-7** and **5-8**.



(5-39) **(5-40)** **(5-41)**

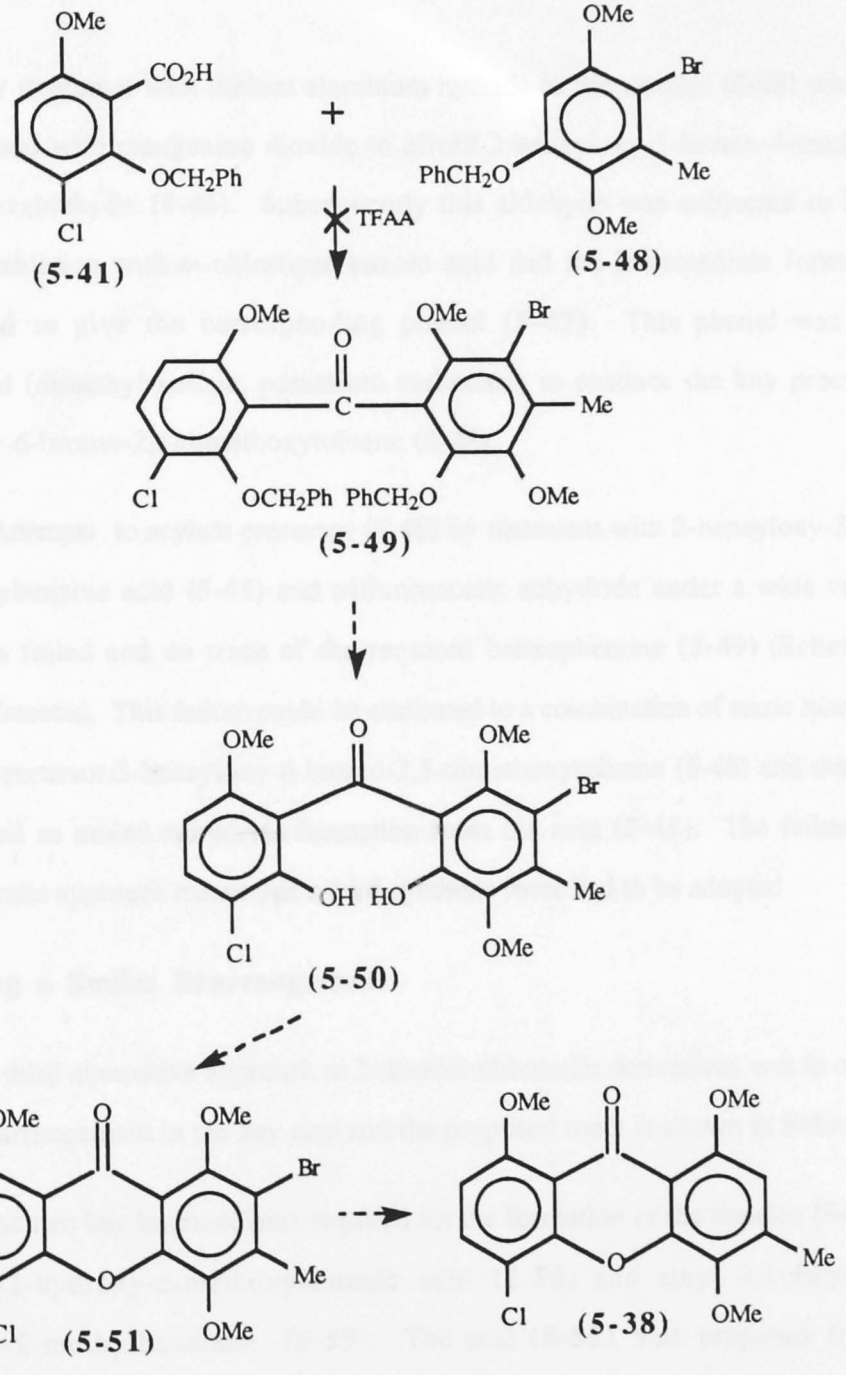
Scheme 5-7



Scheme 5-8

Thus methyl 3-chloro-2-hydroxy-6-methoxybenzoate **(5-39)** (see **iii.** for details of the synthesis and structural confirmation of this compound) was benzylated by treatment with benzyl bromide and potassium carbonate to give methyl 2-benzyloxy-3-chloro-6-methoxybenzoate **(5-40)**, and subsequent alkaline hydrolysis of this ester afforded the acid, 2-benzyloxy-3-chloro-6-methoxybenzoic acid **(5-41)**.

Ethyl everninate[129] (ethyl 2-hydroxy-4-methoxy-6-methylbenzoate) **(5-42)** was used as starting material for the synthesis of the orcinol moiety. Thus bromination of **(5-42)** with one mole of bromine in carbon tetrachloride as described by Sargent[17] gave



Scheme 5-9

ethyl 5-bromo-2-hydroxy-4-methoxy-6-methylbenzoate (**5-43**). Ethyl 5-bromo-2-hydroxy-4-methoxy-6-methylbenzoate (**5-43**) was in turn benzylated to yield 2-benzyloxy-5-bromo-4-methoxy-6-methylbenzoate (**5-44**). The ester (**5-44**) was first

reduced by treatment with lithium aluminum hydride to the alcohol (**5-45**) which was then oxidised with manganese dioxide to afford 2-benzyloxy-5-bromo-4-methoxy-6-methylbenzaldehyde (**5-46**). Subsequently this aldehyde was subjected to Baeyer-Villiger oxidation with *m*-chloroperbenzoic acid and the intermediate formate was hydrolysed to give the corresponding phenol (**5-47**). This phenol was in turn methylated (dimethyl sulfate, potassium carbonate) to produce the key precursor 3-benzyloxy-6-bromo-2,5-dimethoxytoluene (**5-48**).

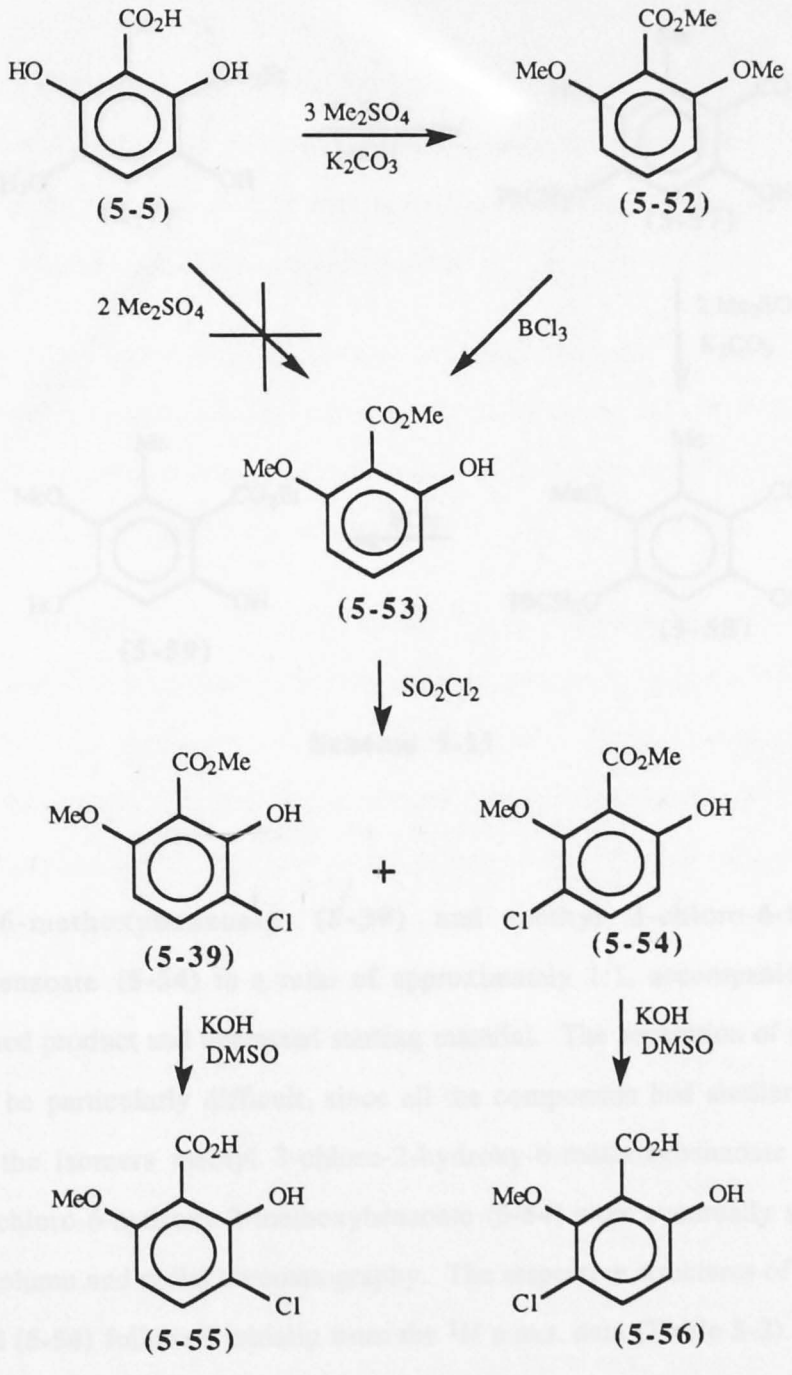
Attempts to acylate precursor (**5-48**) by treatment with 2-benzyloxy-3-chloro-6-methoxybenzoic acid (**5-41**) and trifluoroacetic anhydride under a wide variety of conditions failed and no trace of the required benzophenone (**5-49**) (**Scheme 5-9**) could be detected. This failure could be attributed to a combination of steric hindrance in both the precursor 3-benzyloxy-6-bromo-2,5-dimethoxytoluene (**5-48**) and the acid (**5-41**) as well as mixed anhydride formation from the acid (**5-41**). The failure of this Friedel-Crafts approach meant that a third synthetic route had to be adopted.

iii. Using a Smiles Rearrangement

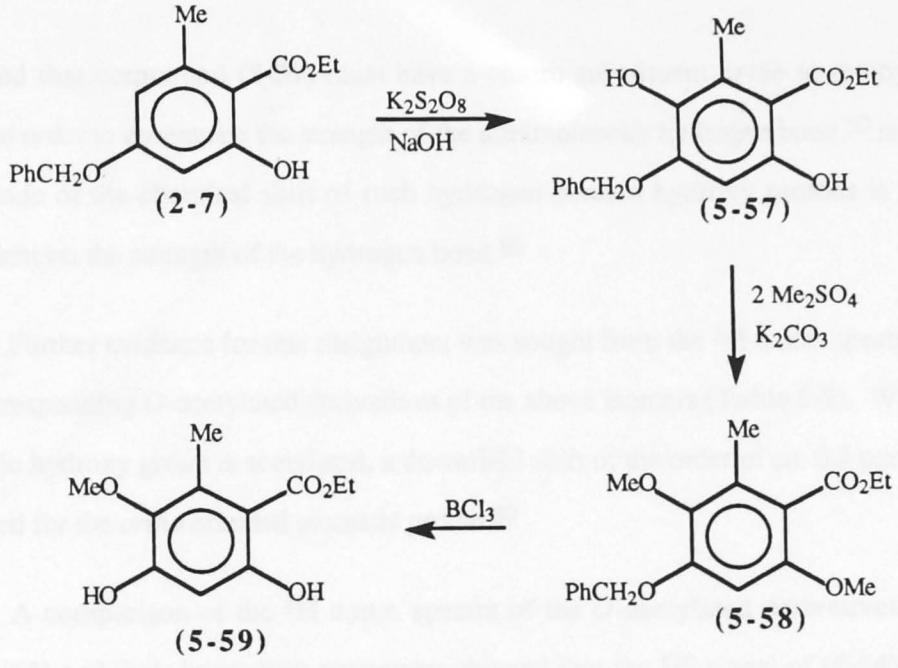
A third alternative approach to 2-dechlorothiomelin derivatives was to utilize the Smiles rearrangement in the key step and the proposed route is shown in **Scheme 5-13**.

The two key intermediates required for the formation of the depside (**5-63**) were 3-chloro-2-hydroxy-6-methoxybenzoic acid (**5-55**) and ethyl 4,6-dihydroxy-3-methoxy-2-methylbenzoate (**5-59**). The acid (**5-55**) was prepared from 2,6-dihydroxybenzoic acid (**5-5**) through a series of steps illustrated in **Scheme 5-10**. While the synthesis of the ester (**5-59**) is depicted in **Scheme 5-11**.

Thus treatment of methyl 2,6-dimethoxybenzoate (**5-52**) with boron trichloride yielded methyl 6-hydroxy-2-methoxybenzoate (**5-53**) in high yield. Chlorination of the ester (**5-53**) with one mole of sulfuryl chloride gave a mixture of methyl 3-chloro-2-


CO2H
HO
OH
3 Me2SO4
K2CO3
CO2Me
MeO
OMe
(5-5)
(5-52)
2 Me2SO4
BCl3
CO2Me
MeO
OH
(5-53)
SO2Cl2
CO2Me
MeO
OH
Cl
+
CO2Me
MeO
OH
Cl
(5-39)
(5-54)
KOH
DMSO
KOH
DMSO
CO2H
MeO
OH
Cl
CO2H
MeO
OH
Cl
(5-55)
(5-56)

Scheme 5-10



Scheme 5-11

hydroxy-6-methoxybenzoate **(5-39)** and methyl 3-chloro-6-hydroxy-2-methoxybenzoate **(5-54)** in a ratio of approximately 1:1, accompanied by some dichlorinated product and unreacted starting material. The separation of this mixture proved to be particularly difficult, since all the compounds had similar R_F values. However the isomers methyl 3-chloro-2-hydroxy-6-methoxybenzoate **(5-39)** and methyl 3-chloro-6-hydroxy-2-methoxybenzoate **(5-54)** were eventually separated by repeated column and radial chromatography. The respective structures of the isomers **(5-39)** and **(5-54)** followed initially from the ^1H n.m.r. data (**Table 5-2**).

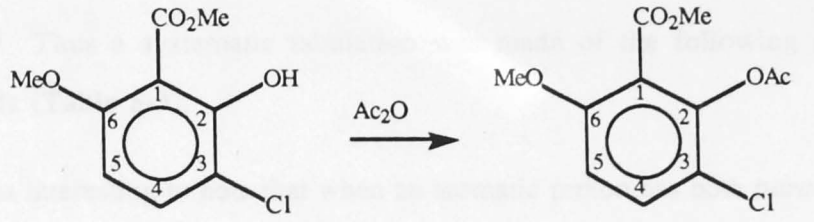
Both compounds exhibited a low field proton signal at *ca.* δ 7.40, assigned to the H4 proton adjacent to the chlorine atom. A comparison of the remaining signals showed that methyl 3-chloro-2-hydroxy-6-methoxybenzoate **(5-39)** exhibited a large downfield shift of the hydroxy resonance (δ 12.01), while methyl 3-chloro-6-hydroxy-2-methoxybenzoate **(5-54)** exhibited a higher field hydroxy resonance (δ 11.09). This

indicated that compound **(5-39)** must have a chloro substituent *ortho* to the hydroxy group in order to accentuate the strength of the intramolecular hydrogen bond,[50] since the magnitude of the chemical shift of such hydrogen bonded hydroxy protons is largely dependent on the strength of the hydrogen bond.[80]

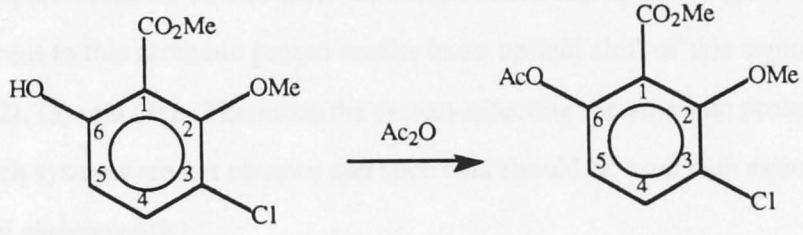
Further evidence for this assignment was sought from the ^{1}H n.m.r. spectra of the corresponding *O*-acetylated derivatives of the above isomers (**Table 5-2**). When a phenolic hydroxy group is acetylated, a downfield shift of the order of *ca.* 0.2 ppm is expected for the *ortho* oriented aromatic proton.[80]

A comparison of the ^{1}H n.m.r. spectra of the *O*-acetylated derivatives **(5-60)** and **(5-61)** and their immediate precursors showed that the H5 signal of **(5-54)** shifted downfield by 0.15 ppm after acetylation (**Table 5-2**), which was in accord with the assigned structures, and in particular, confirmed that H5 of methyl 3-chloro-6-hydroxy-2-methoxybenzoate **(5-54)** was *ortho* to the acetoxy group. *O*-Acetylation was achieved by treating the respective isomers **(5-39)** and **(5-54)** with acetic anhydride and sulfuric acid.

An unexpected observation was noted with the acetylated derivatives **(5-60)** and **(5-61)** (**Table 5-2**). Acetylation of methyl 3-chloro-2-hydroxy-6-methoxybenzoate **(5-39)** caused much more significant downfield shift of H5 (0.4 ppm) than that of the isomer, methyl 3-chloro-6-hydroxy-2-methoxybenzoate **(5-54)** (0.15 ppm). In the former case (i.e. **(5-39)** *cf.* **(5-60)**) the electronic effect of the acetoxy group in the *para*-position, far outweights the anisotropic effect of the acetoxy group in *ortho*-position of the latter (i.e. **(5-54)** *cf.* **(5-61)**).



(5-39) **(5-60)**



(5-54) **(5-61)**

Table 5-2 Proton Chemical Shift Data

Compound	Protons at positions ($CDCl_3$)						
	CO_2Me	OMe	3	4	5	OH	OAc
(5-39)	3.84	3.96	—	7.40	6.38	12.01	—
(5-54)	3.86	4.01	—	7.42	6.74	11.09	—
(5-60)	3.83	3.88	—	7.42	6.78	—	2.29
(5-61)	3.91	3.92	—	7.45	6.89	—	2.25

Another unusual trend was observed when a comparison was made of the chemical shift of the aromatic protons of methyl 3-chloro-2-hydroxy-6-methoxybenzoate **(5-39)** and methyl 3-chloro-6-hydroxy-2-methoxybenzoate **(5-54)**. The former showed a higher field H5 signal (δ 6.38) than the latter (δ 6.74), the reverse of what normally be expected (i.e. an aromatic proton adjacent to an *O*-methyl group would be expected to exhibit a downfield shift by comparison with a proton adjacent to a hydroxy

group).[80] Thus a systematic tabulation was made of the following analogous compounds (**Table 5-3**).

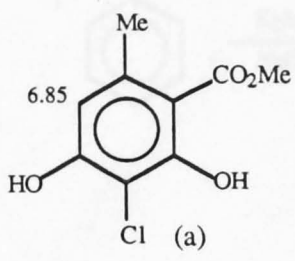
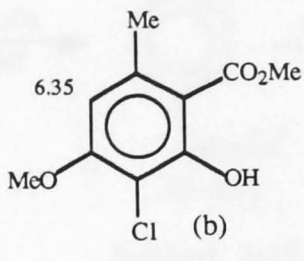
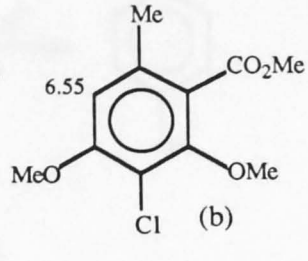
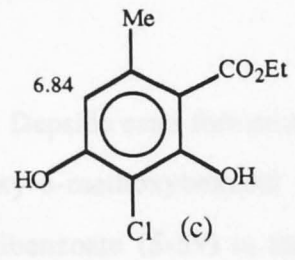
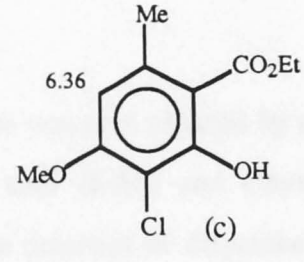
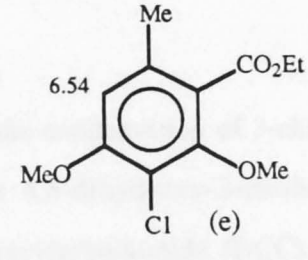
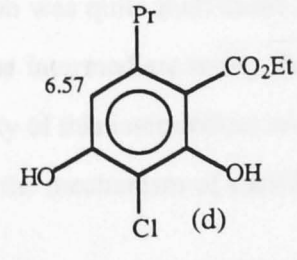
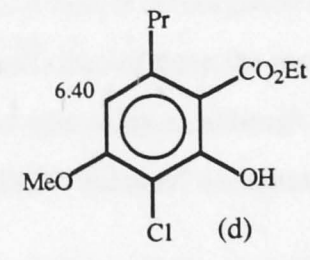
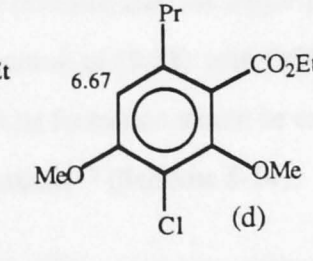
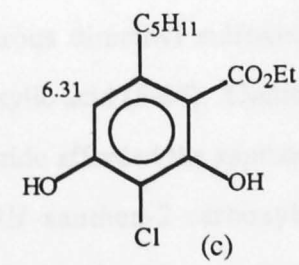
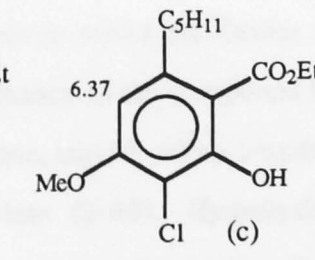
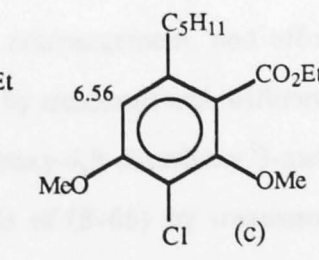
It is interesting to note that when an aromatic proton has both *para* and *ortho* oriented hydroxy groups, 4-*O*-methylation may cause an upfield-shift of this proton signal (compare columns (i) and (ii)). In addition, increasing the length of the carbon chain adjacent to this aromatic proton results in an upfield shift of this signal (compare rows (1), (2), (3) and (4)). Therefore the factors affecting the aromatic proton chemical shifts in such systems are not obvious and such data should be used with extreme caution in structural assignments.

Alkaline hydrolysis of methyl 3-chloro-2-hydroxy-6-methoxybenzoate (**5-39**) led to the formation of the required acid, 3-chloro-2-hydroxy-6-methoxybenzoic acid (**5-55**).

The other mononuclear precursor, ethyl 4,6-dihydroxy-3-methoxy-2-methylbenzoate (**5-59**) (**Scheme 5-11**), had been prepared previously by Elix et al.[36] Ethyl orsellinate was benzylated with benzyl bromide and potassium carbonate to afford the benzyl ether (**2-7**) (**Scheme 2-4**). The additional hydroxy group was then introduced by selective Elbs oxidation of (**2-7**) with alkaline potassium persulfate to yield the corresponding phenol (**5-57**). The selectivity in such oxidations has been attributed[112] to the fact that the intermediate (**5-62**), is more stable under alkaline conditions than the corresponding *ortho* isomer (**Scheme 5-12**).

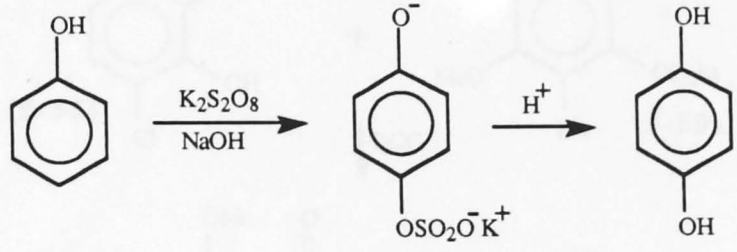
The phenolic compound (**5-57**) thus formed was fully methylated (dimethyl sulfate, potassium carbonate) to give the ester (**5-58**), while subsequent treatment with boron trichloride effected debenzylation and selective demethylation to give the required precursor, ethyl 4,6-dihydroxy-3-methoxy-2-methylbenzoate (**5-59**) (**Scheme 5-11**).

Table 5-3 ^{1}H n.m.r. Chemical Shifts in Some Orsellinic Acid Derivatives

	(i)	(ii)	(iii)
(1)	 (a)	 (b)	 (b)
(2)	 (c)	 (c)	 (e)
(3)	 (d)	 (d)	 (d)
(4)	 (c)	 (c)	 (c)

Sources of Data:

(a) Evans;[52] (b) Birkbeck et al.;[7] (c) Elix et al.;[39] (d) Elix et al.;[50]
(e) remeasured in this work.

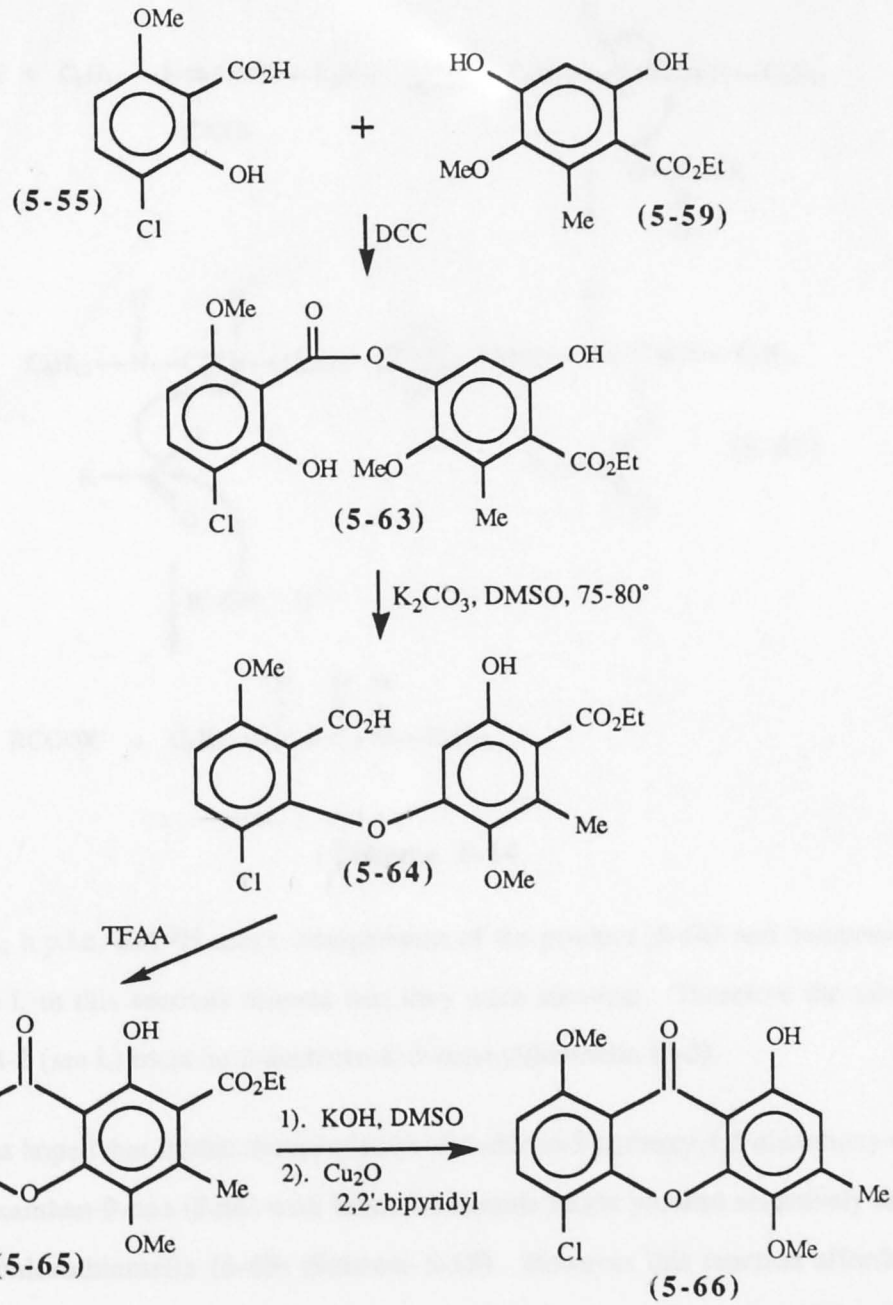


(5-62)

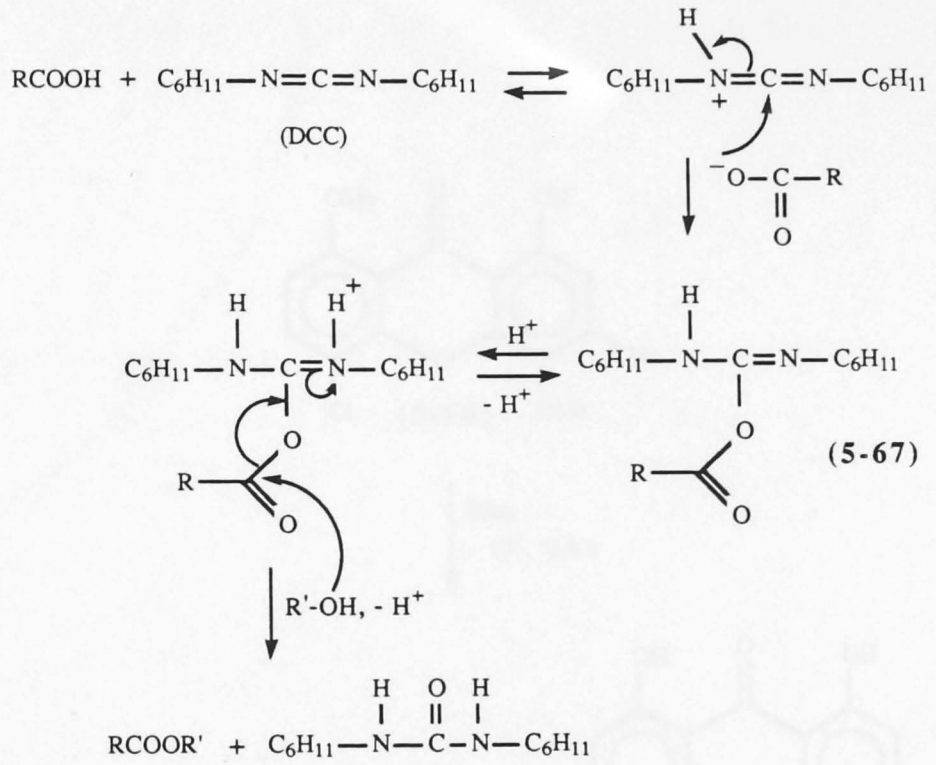
Scheme 5-12

Depside ester formation was then effected by the condensation of 3-chloro-2-hydroxy-6-methoxybenzoic acid (**5-55**) and ethyl 4,6-dihydroxy-3-methoxy-2-methylbenzoate (**5-59**) in the presence of dicyclohexylcarbodiimide (DCC). This reaction was quite inefficient and further investigation revealed that the major product was the intermediate imide (**5-67**) formed from the reaction of (**5-55**) with DCC. The stability of this intermediate was quite unusual, although its formation would be expected given the mechanism of such DCC "induced" condensations[13] (**Scheme 5-14**).

The depside (**5-63**) thus formed was treated with potassium carbonate in anhydrous dimethyl sulfoxide to effect the Smiles rearrangement, and afford the carboxylic acid (**5-64**). Cyclisation of this compound by treatment with trifluoroacetic anhydride afforded the xanthone, ethyl 5-chloro-1-hydroxy-4,8-dimethoxy-3-methyl-9-oxo-9*H*-xanthen-2-carboxylate (**5-65**). Hydrolysis of (**5-65**) by treatment with potassium hydroxide gave the corresponding carboxylic acid, which on decarboxylation with cuprous oxide and 2,2'-bipyridyl afforded 4-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9*H*-xanthen-9-one (**5-66**).


OMe
CO2H
OH
Cl
(5-55)
+
HO
OH
MeO
CO2Et
Me
(5-59)
DCC
OMe
O
O
OH
OH
MeO
CO2Et
Cl
(5-63)
Me
K2CO3, DMSO, 75-80°
OMe
CO2H
OH
CO2Et
O
Me
Cl
(5-64)
OMe
TFAA
OMe
O
OH
CO2Et
1). KOH, DMSO
2). Cu2O
2,2'-bipyridyl
O
Me
Cl
OMe
(5-65)
OMe
O
OH
O
Me
Cl
OMe
(5-66)

Scheme 5-13

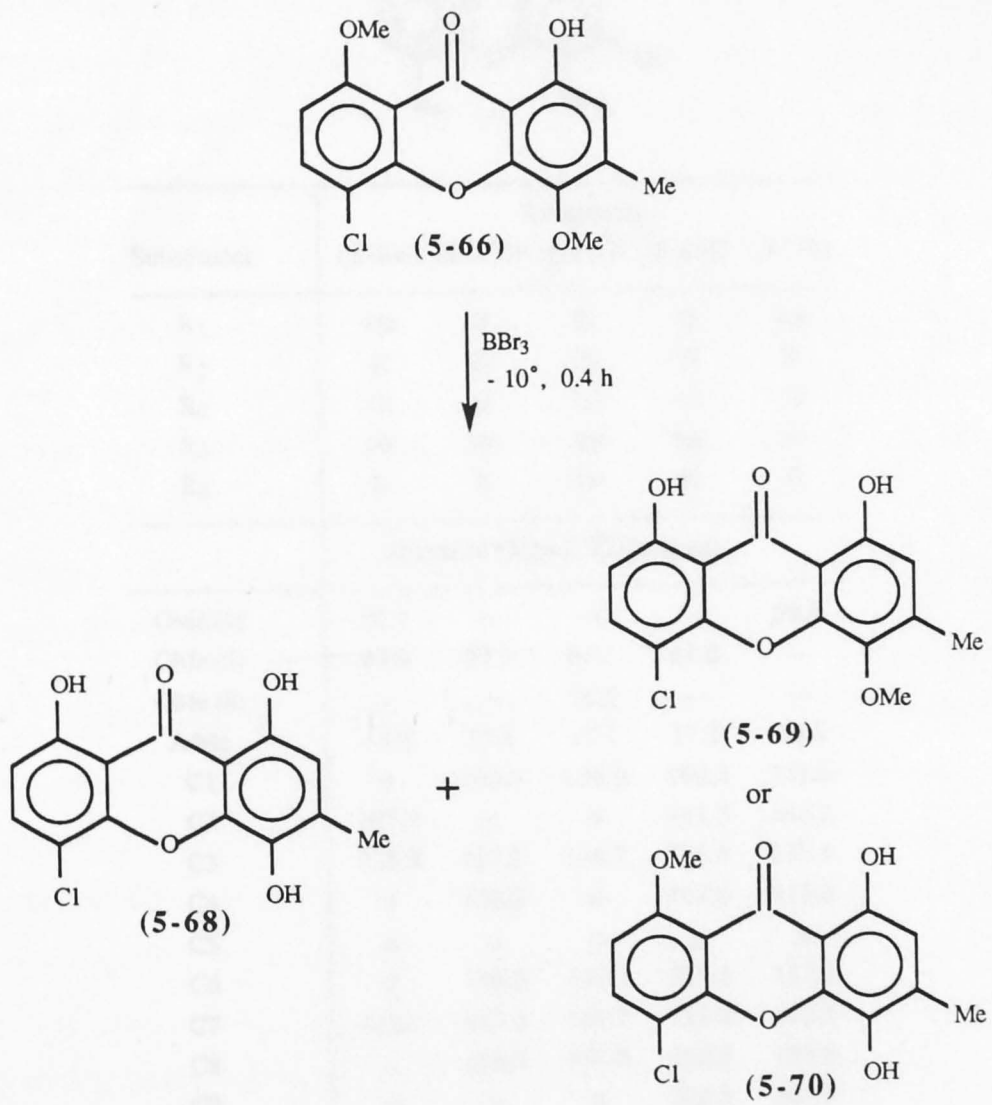


Scheme 5-14

T.l.c., h.p.l.c. and ^{1}H n.m.r. comparisons of the product (**5-66**) and compound **Prod-1** (see **i.** in this section) showed that they were identical. Therefore the other isomer **Prod-2** (see **i.**) must be 2-dechloro-8-*O*-methylthiomelin (**5-3**).

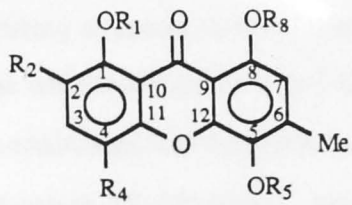
It was hoped that further demethylation of 4-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9*H*-xanthen-9-one (**5-66**) with boron tribromide might proceed selectively and afford 2-dechlorothiomelin (**5-69**) (**Scheme 5-15**). However this reaction afforded two products, 4-chloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthen-9-one (**5-68**) and a corresponding mono-*O*-methyl derivative (either (**5-69**) or (**5-70**)).

This compound was ultimately deduced to have the structure (**5-70**) from ^{13}C n.m.r. comparisons of a series related thiomelin derivatives (**Table 5-4**).


OMe
O
OH
Me
Cl
OMe
(5-66)
BBr3
- 10°, 0.4 h
OH
O
OH
Me
Cl
OMe
(5-69)
or
OH
O
OH
Me
Cl
OH
(5-68)
+
OMe
O
OH
Me
Cl
OH
(5-70)

Scheme 5-15

Table 5-4 ^{13}C n.m.r. Data of Some Thiomelin Derivatives



Substituent	Compound (5-66)	(1-37)[a]	(5-71)[b]	(5-69)[c]	(5-70)
R_1	Me	H	H	H	Me
R_2	H	Cl	Cl	H	H
R_4	Cl	H	Cl	Cl	Cl
R_5	Me	Me	Me	Me	H
R_8	H	H	Me	H	H
	Chemical Shifts ($CDCl_3$, ppm)				
OMe (1)	56.7	—	—	—	56.7
OMe (5)	61.0	61.3	61.1	61.0	—
OMe (8)	—	—	56.5	—	—
ArMe	16.8	17.1	17.1	17.1	16.6
C1	n	156.5	156.0	160.2	159.5
C2	105.9	n	n	111.5	106.2
C3	135.5	137.2	135.7	137.3	135.4
C4	n	108.0	n	111.0	112.0
C5	n	n	n	n	n
C6	n	138.0	141.3	138.1	137.2
C7	112.0	112.1	107.7	112.3	112.2
C8	n	156.2	157.8	156.0	153.6
C9	n	n	n	106.5	107.0
C10	n	n	n	108.4	109.1
C11	n	148.6	n	143.7	152.2
C12	n	142.6	n	151.2	n
C=O	n	185.2	n	185.8	181.4

a. This compound was synthesized in section **5.e.**

b. This compound was isolated by Elix, Gaul et al.[41]

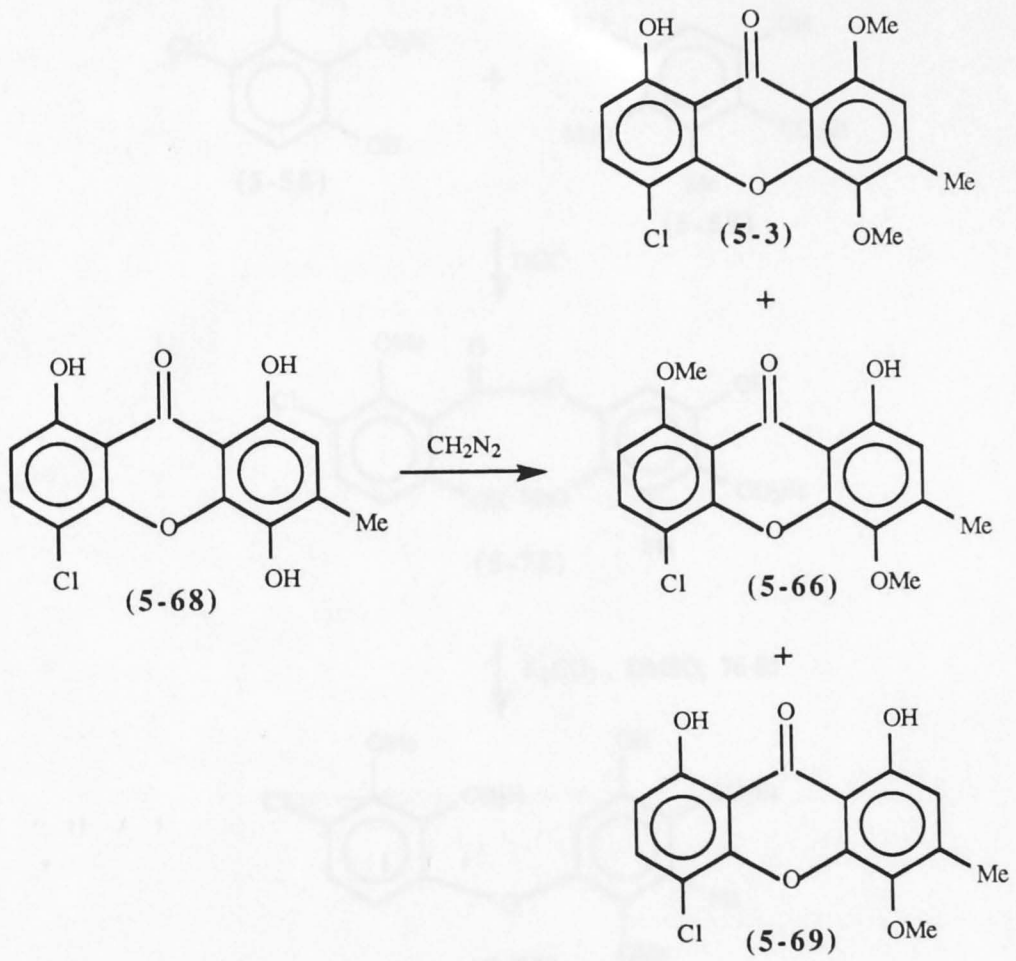
c. This compound was synthesized later in this section.

n. These signals were not observed due to the minute amounts of material available.

All of the compounds with a 8-hydroxy-5-methoxy-6-methyl substitution pattern (i.e. which have the same B-ring structure as (**1-37**)) exhibited a 5-*O*-methyl carbon signal at *ca.* δ 61, while those which have either 1- or 8-*O*-methyl group showed signals at *ca.* δ 56.7. This evidence established that the product obtained by treatment of (**5-66**) with boron tribromide was 4-chloro-5,8-dihydroxy-1-methoxy-6-methyl-9*H*-xanthen-9-one (**5-70**) rather than the required 4-chloro-1,8-dihydroxy-5-methoxy-6-methyl-9*H*-xanthen-9-one (2-dechlorothiomelin) (**5-69**).

Hence the xanthone 4-chloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthen-9-one (**5-68**) was selectively methylated by treatment with diazomethane, and produced 2-dechlorothiomelin (**5-69**) as the major product, accompanied by minor amounts of 4-chloro-1-hydroxy-5,8-dimethoxy-6-methyl-9*H*-xanthen-9-one (**5-3**), 4-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9*H*-xanthen-9-one (**5-66**) and unreacted starting material (**5-68**) (**Scheme 5-16**).

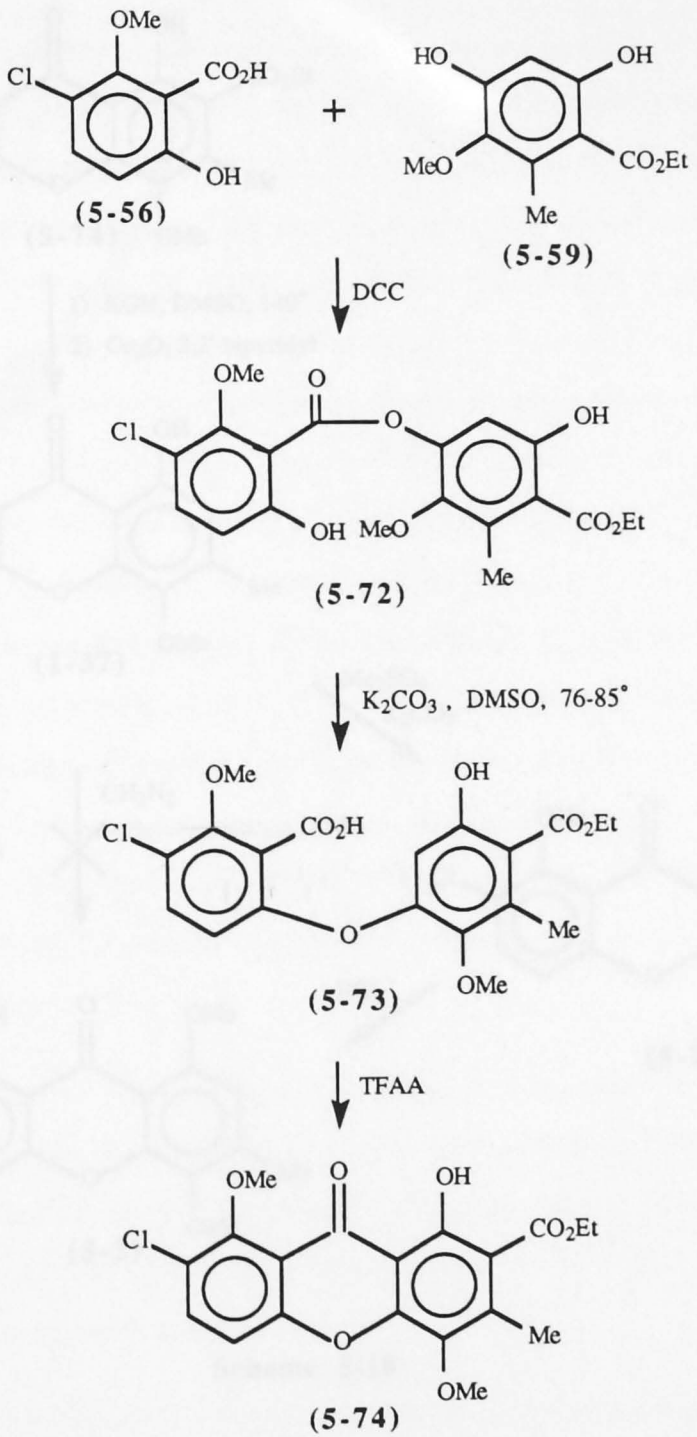
In this reaction, selective methylation occurred at the non-intramolecularly hydrogen bonded hydroxy group of (**5-68**) as expected, but in addition some over-methylated products were also formed. This behaviour is in contrast to that observed for norlichexanthone derivatives[64] but has been recorded with the analogous thiomelin derivatives.[34,97] It can be attributed to the stronger hydrogen bonding of the single hydroxy group *ortho* to the carbonyl goup in the norlichexanthone-type compounds, as opposed to the two competing *ortho*-hydroxy groups in the thiomelin derivatives.[97]



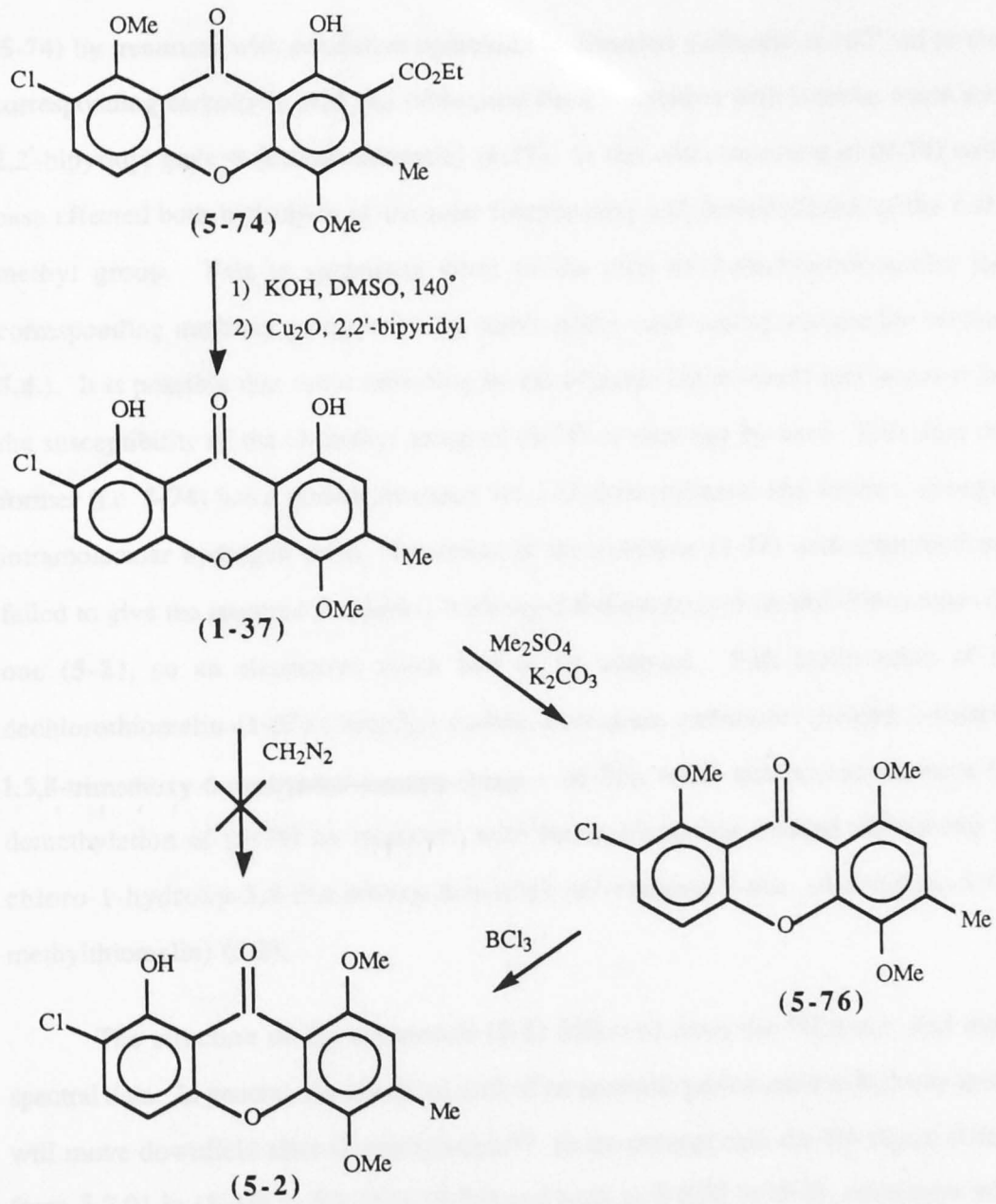
Scheme 5-16

5.e. Synthesis of 4-Dechlorothiomelin (TH1) and Derivatives

4-Dechlorothiomelin (TH1) (**1-37**) was synthesized via a Smiles rearrangement in a manner analogous to that used for preparing 2-dechlorothiomelin (**Schemes 5-17** and **5-18**). The appropriate benzoic acid, 3-chloro-6-hydroxy-2-methoxybenzoic acid (**5-56**), was prepared by hydrolysis of the corresponding methyl ester (**5-54**) as shown in **Scheme 5-10**. This acid (**5-56**) was condensed with ethyl 4,6-dihydroxy-3-methoxy-2-melthylbenzoate (**5-59**) by treatment with DCC. The depside ester (**5-72**)


OMe
Cl
CO2H
OH
(5-56)
+
HO
OH
MeO
CO2Et
Me
(5-59)
DCC
OMe
O
Cl
O
OH
OH
MeO
CO2Et
Me
(5-72)
K2CO3 , DMSO, 76-85°
OMe
OH
Cl
CO2H
CO2Et
O
Me
OMe
(5-73)
TFAA
OMe
O
OH
Cl
CO2Et
O
Me
OMe
(5-74)

Scheme 5-17



Scheme 5-18

so obtained was then subjected to the Smiles rearrangement and subsequent ring-closure to afford the xanthone, ethyl 7-chloro-1-hydroxy-4,8-dimethoxy-3-methyl-9-oxo-9*H*-xanthen-2-carboxylate **(5-74)**, as depicted in **Scheme 5-17**. Hydrolysis of the ester

(**5-74**) by treatment with potassium hydroxide in dimethyl sulfoxide at 140° led to the corresponding carboxylic acid and subsequent decarboxylation with cuprous oxide and 2,2'-bipyridyl gave 4-dechlorothiomelin (**1-37**). In this case, treatment of (**5-74**) with base effected both hydrolysis of the ester functionality and demethylation of the 1-*O*-methyl group. This is surprising since in the case of 2-dechlorothiomelin the corresponding methoxy group was very stable under such conditions (see **i.**in section **5.d.**). It is possible that steric crowding by the adjacent chloro-atom may account for the susceptibility of the *O*-methyl group of (**5-74**) to cleavage by base. Therefore the former (i.e. **5-74**) has a greater tendency for 1-*O*-demethylation and forms a stronger intramolecular hydrogen bond. Treatment of the xanthone (**1-37**) with diazomethane failed to give the required 2-chloro-1-hydroxy-5,8-dimethoxy-6-methyl-9*H*-xanthen-9-one (**5-2**), so an alternative route had to be adopted. Full methylation of 4-dechlorothiomelin (**1-37**) (dimethyl sulfate, potassium carbonate) yielded 2-chloro-1,5,8-trimethoxy-6-methyl-9*H*-xanthen-9-one (**5-76**), while subsequent selective *O*-demethylation of (**5-76**) by treatment with boron trichloride yielded exclusively 2-chloro-1-hydroxy-5,8-dimethoxy-6-methyl-9*H*-xanthen-9-one (4-dechloro-8-*O*-methylthiomelin) (**5-2**).

The structure of the compound (**5-2**) followed from the ^{1}H n.m.r. and mass spectral data. In general, the chemical shift of an aromatic proton *para* to hydroxy group will move downfield after *O*-methylation.[80] In the present case the H4 signal shifted from δ 7.01 in (**1-37**) to δ 7.25 in (**5-76**) and back to δ 6.98 in (**5-2**), consistent with the structural assignments made.

The selectivity of the demethylation of 2-chloro-1,5,8-trimethoxy-6-methyl-9*H*-xanthen-9-one (**5-76**) with boron trichloride (with predominant demethylation of the 1-*O*-methyl group) contrasted with the behaviour of the corresponding 2-dechlorothiomelin derivatives where selective demethylation of the 8-*O*-methyl group predominated.

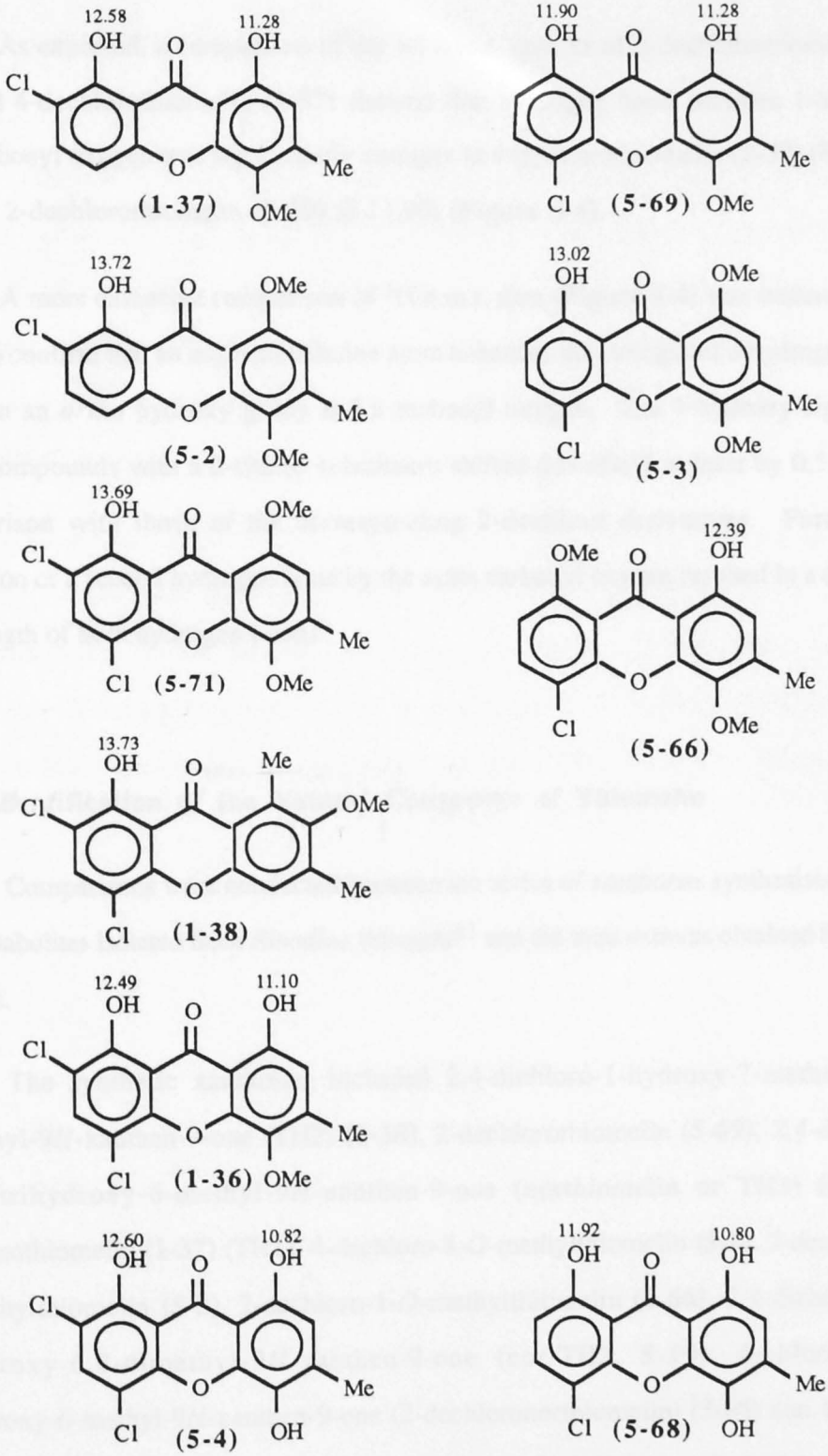

12.58
OH
11.28
OH
O
Cl
Me
(1-37)
OMe
11.90
OH
11.28
OH
O
Me
Cl
(5-69)
OMe
13.72
OH
O
OMe
Cl
Me
(5-2)
OMe
13.02
OH
O
OMe
Me
Cl
OMe
(5-3)
13.69
OH
O
OMe
Cl
Me
Cl
(5-71)
OMe
OMe
O
12.39
OH
Me
O
Cl
OMe
(5-66)
13.73
OH
O
Me
Cl
OMe
Me
Cl
(1-38)
12.49
OH
11.10
OH
O
Cl
Me
Cl
(1-36)
OMe
12.60
OH
O
10.82
OH
Cl
Me
Cl
(5-4)
OH
11.92
OH
O
10.80
OH
Me
Cl
(5-68)
OH

Figure 5-4

As expected, a comparison of the ^{1}H n.m.r. spectra of 2-dechlorothiomelin (**5-69**) and 4-dechlorothiomelin (**1-37**) showed that hydrogen bond between 1-hydroxy and carbonyl oxygen was significantly stronger in 4-dechlorothiomelin (**1-37**) (δ 12.58) than in 2-dechlorothiomelin (**5-69**) (δ 11.90) (**Figure 5-4**).

A more extensive comparison of ^{1}H n.m.r. data (**Figure 5-4**) was undertaken in order to confirm that an adjacent chlorine atom enhances the strength of a hydrogen bond between an *ortho* hydroxy group and a carbonyl oxygen. The 1-hydroxy signals of those compounds with a 2-chloro substituent shifted downfield at least by 0.5 ppm in comparison with those of the corresponding 2-dechloro derivatives. Further the formation of a second hydrogen bond by the same carbonyl oxygen resulted in a decrease in strength of both hydrogen bonds.

5.f. Identification of the Natural Congenors of Thiomelin

Comparisons were conducted between the series of xanthones synthesised above, the metabolites isolated from *Rinodina thiomela*[41] and the total extracts obtained from that species.

The synthetic xanthones included 2,4-dichloro-1-hydroxy-7-methoxy-6,8-dimethyl-9*H*-xanthen-9-one (TH2) (**1-38**), 2-dechlorothiomelin (**5-69**), 2,4-dichloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthen-9-one (northiomelin or TH3) (**5-4**), 4-dechlorothiomelin (**1-37**) (TH1), 4-dechloro-8-*O*-methylthiomelin (**5-2**), 2-dechloro-8-*O*-methylthiomelin (**5-3**), 2-dechloro-1-*O*-methylthiomelin (**5-66**), 2,4-dichloro-1,7-dihydroxy-6,8-dimethyl-9*H*-xanthen-9-one (nor-TH2, **5-19**), 4-chloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthen-9-one (2-dechloronorthiomelin) (**5-68**) and 4-chloro-5,8-dihydroxy-1-methoxy-6-methyl-9*H*-xanthen-9-one (2-dechloro-1-*O*-methylnorthiomelin) (**5-70**). Authentic samples of thiomelin (**1-36**) and 8-*O*-

methylthiomelin were also available[41] and were compared with the total extracts of *R. thiomela.*

Direct comparisons between the natural products isolated from *R. thiomela* (i.e. 4-dechlorothiomelin (**1-37**), xanthone TH2 (**1-38**), 4-dechloro-8-*O*-methylthiomelin (**5-2**), and 2-dechloro-8-*O*-methylthiomelin (**5-3**)) and the corresponding synthetic materials were conducted using spectroscopy (^{1}H n.m.r., mass spectra), chromatographic comparisons (t.l.c., h.p.l.c.) and physical properties (melting points, mixed melting points), and confirmed their identity.

Those substances which were present in the lichen in minor (or trace) amounts were not isolated, but comparisons were conducted by high performance t.l.c. (using four independent solvent systems) and comparative h.p.l.c. By this means, the natural occurrence of 2-dechlorothiomelin (**5-69**), northiomelin (TH3, **5-4**), and 2,4-dichloro-1,7-dihydroxy-6,8-dimethyl-9*H*-xanthen-9-one (nor-TH2, **5-19**) were confirmed.

Chapter 6. Experimental

6.1. General

^{1}H n.m.r. spectra were recorded at 300 MHz on Varian VXR 300S, or on Varian Gemini 300, at 200 MHz on Varian XL 200E, at 80 MHz on Varian CFT-20, and at 60 MHz on Varian EM 360A spectrometers. ^{13}C n.m.r. spectra were recorded at 70 MHz on Varian VXR 300S and at 50.1 MHz on Varian XL 200E spectrometers. Chemical shifts are expressed in ppm (δ) relative to tetramethylsilane (TMS) as internal standard. Mass spectra were recorded using EI at 70 eV on a VG-Micromass 7070F mass spectrometer linked on line to a Finnigan Incos data system. Melting points are uncorrected. Microanalyses were carried out by the A.N.U. Microanalytical Service Unit. H.p.l.c. was carried out on a Perkin-Elmer C-18 HS-5 h.p.l.c. column with 10% water / methanol containing orthophosphoric acid (80 µl / 400 ml) at a flow rate of 0.6 ml min^{-1}. Compounds were detected by UV absorption at 254 nm. Retention index (RI) values are relative to salazinic acid (R_t 3.40 min) and atranorin (R_t 7.34 min).[77] Standard h.p.l.c. R_F values were determined in four independent t.l.c. solvent systems:[46,47] (A) toluene / dioxan / acetic acid (180 : 45 : 5); (B) hexane / methyl t-butyl ether / formic acid (140 : 72 : 18); (C) toluene / acetic acid (170 : 30); (E) ethyl acetate / cyclohexane (1 : 3); and (F) ethyl acetate / cyclohexane (1 : 1). The chromatotron refers to the radial chromatography using a Chromatotron Model 7904 and SiO_2 60 PF_{254} plates. Light petroleum refers to the fraction boiling between 60° and 80°.

6.2. Synthesis of Norlichexanthones via a Smiles Rearrangement

6.2.a. Synthesis of 7-Chloronorlichexanthone

Ethyl 4-Benzyloxy-2-hydroxy-6-methylbenzoate **(2-7)**

A mixture of ethyl orsellinate **(2-6)** (10 g, 51 mmol), benzyl bromide (6.1 ml, 51 mmol), and potassium carbonate (17.8 g, 130 mmol) in acetone (110 ml) was stirred at room temperature for 24 h. The mixture was then poured into cold diluted hydrochloric acid and extracted with ether. The ether layer was washed with water and brine and dried ($MgSO_4$). The crude product was then purified by flash chromatography[116] (SiO_2) using 1.8% ethyl acetate / light petroleum as eluant to give ethyl 4-benzyloxy-2-hydroxy-6-methylbenzoate **(2-7)** (6.8 g, 47%), which crystallized from cyclohexane as colourless needles, m.p. 53° (lit.[17] m.p. 53-54°).

Ethyl 4-Benzyloxy-3-chloro-6-hydroxy-2-methylbenzoate **(2-8)**

A solution of sulfuryl chloride (1.9 g, 14 mmol) in anhydrous ether (30 ml) was added dropwise to a stirred solution of ethyl 4-benzyloxy-2-hydroxy-6-methylbenzoate **(2-7)** (4 g, 14 mmol) in anhydrous diethyl ether (59 ml) at 17° for 17 h. Evaporation of the solvent under reduced pressure gave the crude product which was crystallized from dichloromethane to give *ethyl 4-benzyloxy-3-chloro-6-hydroxy-2-methylbenzoate* **(2-8)** (2.9 g, 64%) as colourless prisms, m.p. 112-113° (Found: C, 63.6; H, 5.5; Cl, 10.9. $C_{17}H_{17}O_4Cl$ requires: C, 63.7; H, 5.3; Cl, 11.1%). ^1H n.m.r. ($CDCl_3$) δ 1.40, 3H, t, *J* 7Hz, CH_2CH_3; 2.65, 3H, s, ArMe; 4.35, 2H, q, *J* 7Hz, CH_2CH_3; 5.13, 2H, s, CH_2Ph; 6.41, 1H, s, ArH; 7.40, 5H, m, Ph. Mass spectrum *m/z* 322 (2.9%), 320 (M, 7.4), 276 (2.6), 274 (7.6), 91 (100).

4-Benzyloxy-3-chloro-6-hydroxy-2-methylbenzoic Acid **(2-9)**

A mixture of ethyl 4-benzyloxy-3-chloro-6-hydroxy-2-methylbenzoate **(2-8)** (1.90 g, 5.9 mmol), dimethyl sulfoxide (29 ml), potassium hydroxide (1.3 g) and water (6 ml) was stirred and heated at 98° for 4 h, then cooled, diluted with water and extracted with ether to remove any unchanged starting material. The basic aqueous layer was poured into cold dilute hydrochloric acid, extracted with ether and the ethereal extract washed with water, saturated brine, and then dried ($MgSO_4$). After removal of solvent the residue was crystallized from cyclohexane to give *4-benzyloxy-3-chloro-6-hydroxy-2-methylbenzoic acid* **(2-9)** (0.89 g, 51%) as colourless crystals, m.p. 221-222° (Found: C, 61.3; H, 4.3; Cl, 12.5. $C_{15}H_{13}O_4Cl$ requires: C, 61.6; H, 4.5; Cl, 12.1%). ^1H n.m.r. ($CDCl_3$) δ 2.71, 3H, s, Me; 5.22, 2H, s, CH_2Ph; 6.55, 1H, s, ArH; 7.42, 5H, m, Ph. Mass spectrum *m/z* 294 (0.5%), 292 (M, 1.3), 248 (1.2), 91 (100).

Benzyl 2,4,6-Trihydroxybenzoate **(2-11)**

A mixture of 2,4,6-trihydroxybenzoic acid **(2-10)** (6.7 g, 39.4 mmol), benzyl bromide (5 ml, 39.4 mmol) and potassium hydrogen carbonate (10 g) in *N,N*-dimethylacetamide (100 ml) was stirred at room temperature for 16 h. The reaction mixture was then diluted with ethyl acetate (400 ml) and water (400 ml). The organic layer was separated, washed with water, saturated brine and dried ($MgSO_4$). The solvent was evaporated and the residue crystallized from ethanol / water to give *benzyl 2,4,6-trihydroxybenzoate* **(2-11)** (7.6 g, 74%) as colourless crystals, m.p. 127-128° (Found: C, 60.4; H, 5.0. $C_{14}H_{12}O_5$ requires: C, 60.4; H, 5.1%). ^1H n.m.r. ($CDCl_3$) δ 5.58, 2H, s, CH_2Ph; 5.95, 2H, s, ArH; 7.50, 5H, m, Ph; 9.43, 1H, s, OH; 10.03, 2H, s, OH. Mass spectrum *m/z* 260 (M, 3.1%), 91 (100).

Benzyl 3-Chloro-2,4,6-trihydroxybenzoate **(2-12)**

A solution of sulfuryl chloride (2.7 g, 20 mmol) in anhydrous ether (40 ml) was added dropwise to a solution of benzyl 2,4,6-trihydroxybenzoate **(2-11)** (5.2 g, 20 mmol) in anhydrous ether (80 ml). The mixture was then stirred at room temperature for 17 h. Evaporation of the solvent under reduced pressure gave the crude product which was purified by column chromatography (SiO_2) using 10-14 % ethyl acetate / light petroleum as eluant to give *benzyl 3-chloro-2,4,6-trihydroxybenzoate* **(2-12)** (5.5 g, 93%) as colourless prisms, m.p. 125-126° (Found: C, 57.3; H, 3.9; Cl, 11.7. $C_{14}H_{11}O_5Cl$ requires: C, 57.1; H, 3.8; Cl, 12.0%). ^1H n.m.r. ($CDCl_3$) δ 5.48, 2H, s, CH_2Ph; 6.19, 1H, s, ArH; 7.42, 5H, m, Ph; 9.67, 10.34 and 10.49, each 1H, s, OH. Mass spectrum *m/z* 296 (0.5%), 294 (M, 1.2), 204 (1.1), 91 (100.0).

Benzyl 4-(4'-Benzyloxy-3'-chloro-6'-hydroxy-2'-methylbenzoyloxy)-2,6-dihydroxybenzoate **(2-13)**

A mixture of 4-benzyloxy-3-chloro-6-hydroxy-2-methylbenzoic acid **(2-9)** (1.45 g, 5 mmol) and benzyl 2,4,6-trihydroxybenzoate **(2-11)** (1.30 g, 5 mmol) were dried by azeotropic distillation with toluene. Then the mixture was dissolved in toluene (25 ml) and trifluoroacetic anhydride (5 ml) and stirred at room temperature for 24 h. The solvent was then evaporated and the product crystallized from ethyl acetate to give the *depside* **(2-13)** (1.2 g, 44%) as colourless crystals, m.p. 143-144° (Found: C, 65.5; H, 4.4; Cl, 6.9. $C_{29}H_{23}O_8Cl$ reqires: C, 65.1; H, 4.3; Cl, 6.6%). ^1H n.m.r. ($CDCl_3$) δ 2.73, 3H, s, Me; 5.18, 2H, s, $ArOCH_2Ph$; 5.51, 2H, s, CO_2CH_2Ph; 6.35, 2H, s, H3 and H5; 6.50, 1H, s, H5'; 7.40, 10H, m, Ph; 9.90, 2H, s, OH; 11.08, 1H, s, OH. Mass spectrum *m/z* 280 (0.2%), 278 (0.4), 260 (2.7%), 231 (2.2), 153 (1.2), 149 (2.1), 91 (100.0).

Benzyl 6-Benzyloxy-7-chloro-1,3-dihydroxy-8-methyl-9-oxo-9H-xanthen-2-carboxylate **(2-17)**

A solution of benzyl 4-(4'-benzyloxy-3'-chloro-6'-hydroxy-2'-methylbenzoyloxy)-2,6-dihydroxybenzoate **(2-13)** (1.1 g, 2.06 mmol) and anhydrous potassium carbonate (0.45 g, 3.3 mmol) in anhydrous dimethyl sulfoxide (22 ml) was stirred at room temperature for 2 h. The reaction mixture was then acidified with cold dilute hydrochloric acid, extracted with ethyl acetate, and the ethyl acetate extract washed with water, brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product, *4-benzyloxy-2-(4'-benzyloxycarbonyl-3',5'-dihydroxyphenoxy)-5-chloro-6-methylbenzoic acid* **(2-15)** (0.9 g, 80%) as a brown gum. ^1H n.m.r. ($CDCl_3$) δ 2.48, 3H, s, Me; 5.06, 2H, s, $ArOCH_2Ph$; 5.46, 2H, s, CO_2CH_2Ph; 5.99, 2H, s, H2' and H6'; 6.54, 1H, s, H3; 7.42, 10H, m, Ph. Mass spectrum *m/z* 392 (1.5%), 391 (7.9), 377 (0.9), 363 (0.9), 282 (1.0), 280 (0.9), 279 (4.3), 272 (2.5), 249 (1.1), 247 (10.1), 241 (2.7), 227 (6.4), 223 (4.3), 220 (2.0), 211 (3.0), 200 (39.6), 183 (11.1), 168 (42.0), 167 (48.9), 148 (11.7), 136 (11.4), 134 (48), 127 (48.0), 117 (100).

The carboxylic acid **(2-15)** (0.9 g, 1.7mmol) was then dried by azeotropic distillation with toluene and then dissolved in anhydrous toluene (21 ml), cooled and stirred at 0°. Trifluoroacetic anhydride (4.1 ml) was then added and the mixture was stirred first at 0° for 10 min, then at room temperature for 22 h. The product was filtered and washed with hot ethyl acetate / cyclohexane to give *benzyl 6-benzyloxy-7-chloro-1,3-dihydroxy-8-methyl-9-oxo-9H-xanthen-2-carboxylate* **(2-17)** (0.52 g, 59%) as a colourless microcrystalline solid, m.p. 241-242° (Found: mol. wt. 516.0977. $C_{29}H_{21}O_7{}^{35}Cl$ requires: mol. wt. 516.0976). ^1H n.m.r. ($CDCl_3$) δ 3.01, 3H, s, Me; 5.26, 2H, s, $ArOCH_2Ph$; 5.48, 2H, s, CO_2CH_2Ph; 6.27, 1H, s, H4; 6.81, 1H, s, H5; 7.42, 10H, m, Ph; 12.55 and 13.12, each 1H, s, OH. Mass spectrum *m/z* 518 (0.2%), 516 (M, 0.7), 500 (0.2), 498 (0.7), 91 (100.0).

*7-Chloro-1,3,6-trihydroxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylic Acid* **(2-19)**

A solution of benzyl 6-benzyloxy-7-chloro-1,3-dihydroxy-8-methyl-9*H*-xanthen-9-one-2-carboxylate **(2-17)** (0.1 g, 0.19 mmol) in anhydrous dichloromethane (16 ml) was treated with a solution of boron trichloride in dichloromethane (1 M, 1.8 ml) and the mixture stirred at room temperature for 3 h. The mixture was then poured into a mixture of ice and water, concentrated to remove the dichloromethane solvent, and the solid filtered and washed with water. The yellow residue was recrystallized from dimethylformamide to give *7-chloro-1,3,6-trihydroxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylic acid* **(2-19)** (0.06 g, 93%) as yellow needles, which decomposed at 360° (Found: mol. wt. 336.0036. $C_{15}H_9O_7{}^{35}Cl$ requires: mol. wt. 336.0036). ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2.86, 3H, s, Me; 6.32, 1H, s, H4; 6.88, 1H, s, H5. Mass spectrum *m/z* 336 (M, 1.43%), 294 (32.0), 292 (100.0).

*6-Benzyloxy-7-chloro-1,3-dihydroxy-8-methyl-9*H*-xanthen-9-one* **(2-20)**

A mixture of the above benzyl 6-benzyloxy-7-chloro-1,3-dihydroxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylate **(2-17)** (0.3 g, 0.58 mmol), dimethyl sulfoxide (4.2 ml), potassium hydroxide (0.5 g) and water (1 ml) was stirred and heated under a nitrogen atmosphere at 100-110° for 5 h, and then diluted with water. The basic aqueous solution was poured into cold, dilute hydrochloric acid, extracted with ethyl acetate and the organic extract washed with water, saturated brine, and then dried ($MgSO_4$). After removal of the solvent the residue was purified by radial chromatography (SiO_2) using 2-40 % ethyl actate / light petroleum as eluant to give *6-benzyloxy-7-chloro-1,3-dihydroxy-8-methyl-9*H*-xanthen-9-one* **(2-20)** (0.1 g, 45%) as pale brown plates, m.p. 290-292° (Found: mol. wt. 382.0607. $C_{21}H_{15}O^{35}Cl$ requires: mol. wt. 382.0608). ^{1}H n.m.r. ($CDCl_3$) δ 3.02, 3H, s, Me; 5.24, 2H, s, CH_2Ph; 6.27, 2H, s, H2 and H4; 6.81, 1H,

s, H5; 7.42, 5H, m, Ph. Mass spectrum *m/z* 384 (13.4%), 382 (M, 35.6), 294 (1.7), 292 (5.1), 91 (100.0).

*7-Chloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (7-Chloronorlichexanthone)* **(2-21)**

Method I

A solution of 6-benzyloxy-7-chloro-1,3-dihydroxy-8-methyl-9*H*-xanthen-9-one **(2-20)** (0.1 g, 0.26 mmol) in anhydrous dichloromethane (30 ml) was treated with a solution of boron trichloride (2 mmol) in dichloromethane (2 ml) and the mixture was stirred at room temperature for 2 h. The mixture was then poured into a mixture of ice and water, extracted with chloroform and the organic layer washed with saturated sodium hydrogen carbonate solution, water, saturated brine and then dried ($MgSO_4$). After removal of the solvent the residue was purified by radial chromatography over silica gel using ethyl acetate / light petroleum as eluant to give 7-chloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one **(2-21)** (0.062 g, 81%) as pale yellow-brown crystals, m.p. 284-285° (lit.[79] m.p. 285-286°) identical with the authentic material (t.l.c., h.p.l.c.). ^{1}H n.m.r. ($CDCl_3$) δ 2.98, 3H, s, Me; 6.21, 1H, d, *J* 2Hz, H2; 6.25, 1H, d, *J* 2Hz, H4; 6.96, 1H, s, H5. Mass spectrum *m/z* 294 (35.5%), 292 (M, 100), 257 (7.0). Standard t.l.c. R_F values: R_F (A) 0.72; R_F (B) 0.61; R_F (C) 0.76; R_F (E) 0.42; R_F (F) 0.78. Standard h.p.l.c. RI value: 0.39.

Method II

A mixture of 7-chloro-1,3,6-trihydroxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylic acid **(2-19)** (0.15 g, 0.446 mmol), dimethyl sulfoxide (3 ml), potassium hydroxide (0.38 g) and water (1 ml) was stirred and heated at 100-110° for 5 h, and then diluted with water. The basic aqueous layer was poured into cold, dilute hydrochloric

acid, extracted with ethyl acetate and the organic extract washed with water, saturated brine and then dried ($MgSO_4$). After removal of the solvent the residue was crystallized from ethyl acetate / cyclohexane to yield 7-chloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one **(2-21)** (0.1 g, 76%) identical with the above material.

6.2.b. Synthesis of 2,7-Dichloronorlichexanthone, 4,7-Dichloronorlichexanthone and 2,4,7-Trichloronorlichexanthone

*2,7-Dichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (2,7-Dichloronorlichexanthone)* **(2-22)** *and 4,7-Dichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (4,7-Dichloronorlichexanthone)* **(2-23)**

7-Chloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one **(2-21)** (0.1 g, 0.34 mmol), *N*-chlorosuccinimide (0.051 g), several crystals of toluene-4-sulphonic acid and dioxan (12 ml) were heated under reflux for 20 h. The solution was then poured into water and extracted with ethyl acetate. The organic extract was washed with water, brine and dried ($MgSO_4$). The crude product obtained on evaporation of the solvent was purified by radial chromatography (SiO_2) using 40% ethyl acetate / light petroleum as eluant. The faster moving band yielded 4,7-dichloro-8-methyl-1,3,6-trihydroxy-9*H*-xanthen-9-one **(2-23)** (0.03 g, 27%) as yellow crystals, m.p. 297-298° (lit.[122] m.p. 290-293°) (Found: mol. wt. 325.9748. $C_{14}H_8O_5{}^{35}Cl_2$ reqires: mol. wt. 325.9749). ^1H n.m.r. [$(CD_3)_2CO$] δ 2.93, 3H, s, Me; 6.35, 1H, s, H2; 6.97, 1H, s, H5; 9.64, 1H, s, OH. Mass spectrum *m/z* 328 (0.5%), 326 (M, 1.0), 294 (0.2), 292 (0.7), 45 (100.0). Standard t.l.c. R_F values: R_F (A) 0.43; R_F (B) 0.47; R_F (C) 0.32; R_F (F) 0.52. Standard h.p.l.c. RI value: 0.57.

The slower moving band contained the isomer, 2,7-dichloro-8-methyl-1,3,6-trihydroxy-9*H*-xanthen-9-one **(2-22)** (0.012 g, 11%) as yellow crystals, m.p. 296-298°

(lit.[122] m.p. 298-299°) (Found: mol. wt. 325.9748. $C_{14}H_8O_5{}^{35}Cl_2$ reqires: mol. wt. 325.9749). ^1H n.m.r. [$(CD_3)_2CO$] δ 2.95, 3H, s, Me; 6.50, 1H, s, H4; 6.91, 1H, s, H5; 8.85, 1H, s, OH. Mass spectrum *m/z* 330 (3.5%), 328 (19.6), 326 (M, 30.5), 294 (24.2), 292 (69.3), 43 (100.0). Standard t.l.c. R_F values: R_F (A) 0.40; R_F (B) 0.38; R_F (C) 0.27; R_F (F) 0.26. Standard h.p.l.c. RI value: 0.49. The t.l.c. and h.p.l.c. behaviour of synthetic **(2-22)** was identical with that of one of the minor metabolites of the lichen *Lecanora broccha* from Argentina and an Australian *Buellia* species.[37]

Benzyl 4-(4'-Benzyloxy-3'-chloro-6'-hydroxy-2'-methylbenzoyloxy)-3-chloro-2,6-dihydroxybenzoate **(2-14)**

A mixture of 4-benzyloxy-3-chloro-6-hydroxy-2-methylbenzoic acid **(2-9)** (1.45 g, 5 mmol) and benzyl 3-chloro-2,4,6-trihydroxybenzoate **(2-12)** (1.38 g, 5 mmol) were dried by azeotropic distillation with toluene. The mixture was then dissolved in toluene (25 ml) and trifluoroacetic anhydride (5 ml) and stirred at room temperature for 24 h. The solvent was then evaporated and the product crystallized from ethyl acetate to give *benzyl 4-(4'-benzyloxy-3'-chloro-6'-hydroxy-2'-methylbenzoyloxy)-3-chloro-2,6-dihydroxy-benzoate* **(2-14)** (1.2 g, 42%) as colourless crystals, m.p. 156-157° (Found: C, 60.1; H,4.3; Cl, 7.7. $C_{29}H_{22}O_8Cl_2$ requires: C, 60.2; H, 4.2; Cl, 7.7%). ^1H n.m.r. ($CDCl_3$) δ 2.72, 3H, s, Me; 4.92, 2H, s, $ArOCH_2Ph$; 5.51, 2H, s, CO_2CH_2Ph; 6.36 and 6.45, each 1H, s, ArH; 7.42, 10H, m, Ph; 9.87, 2H, s, OH; 11.05, 1H, s, OH. Mass spectrum *m/z* 391 (2.8%), 351 (5.9), 261 (100.0).

*Benzyl 6-Benzyloxy-4,7-dichloro-1,3-dihydroxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylate* (**2-18**)

A solution of benzyl 4-(4'-benzyloxy-3'-chloro-6'-hydroxy-2'-methylbenzoyloxy)-3-chloro-2,6-dihydroxybenzoate (**2-14**) (0.61 g, 1.07 mmol) and anhydrous potassium carbonate (0.23 g 1.7 mmol) in anhydrous dimethyl sulfoxide (11 ml) was stirred at room temperature for 2 h. The reaction mixture was then acidified with cold dilute hydrochloric acid, extracted with ethyl acetate, and the ethyl acetate extract washed with water and brine and dried ($MgSO_4$). Evaporation of the solvent gave the crude *4-benzyloxy-2-(4'-benzyloxycarbonyl-2'-chloro-3',5'-dihydroxyphenoxy)-5-chloro-6-methylbenzoic acid* (**2-16**) (0.59 g, 96%) as a pale brown microcrystalline solid. ^{1}H n.m.r. ($CDCl_3$) δ 2.50, 3H, s, Me; 5.07, 2H, s, $ArOCH_2Ph$; 5.49, 2H, s, CO_2CH_2Ph; 5.85 and 6.50, each 1H, s, ArH; 7.35 and 7.42, each 5H, m, Ph; 9.75 and 10.39, each 1H, s, OH.

The carboxylic acid (**2-16**) (0.59 g, 1.04 mmol) was then dried by azeotropic distillation with toluene and then dissolved in anhydrous toluene (21 ml) and cooled and stirred at 0°. Trifluoroacetic anhydride (3.6 ml) was then added and the mixture was stirred at 0° for 10 min, then at room temperature for 22 h. The solvent was then removed and the product crystallized from ethyl acetate / cyclohexane to give *benzyl 6-benzyloxy-4,7-dichloro-1,3-dihydroxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylate* (**2-18**) (0.5 g, 87%) as a pale yellow solid, m.p. 256-257° (Found: mol. wt. 550.0587. $C_{29}H_{20}O_7{}^{35}Cl_2$ requires: mol. wt. 550.0586). ^{1}H n.m.r. ($CDCl_3$) δ 3.02, 3H, s, Me; 5.29, 2H, s, $ArOCH_2Ph$; 5.50, 2H, s, CO_2CH_2Ph; 6.99, 1H, s, ArH; 7.43, 10H, m, Ph. Mass spectrum *m/z* 552 (0.2%), 550 (M, 0.2), 446 (0.1), 444 (0.7), 442 (0.9), 108 (21.9), 91 (100.0).

*4,7-Dichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (4,7-Dichloronorlichexanthone)* **(2-23)**

A mixture of the above benzyl ester **(2-18)** (0.36 g, 0.653 mmol), dimethyl sulfoxide (4.7 ml), potassium hydroxide (0.56 g) and water (1 ml) was stirred in a nitrogen atmosphere and heated under reflux for 45 min, and then diluted with water. The basic aqueous layer was poured into cold, dilute hydrochloric acid, extracted with ethyl acetate and the organic extract washed with water, saturated brine and then dried ($MgSO_4$). After removal of the solvent the residue was purified by radial chromatography (SiO_2) using 5-70% ethyl acetate / light petroleum as eluant to give 4,7-dichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one **(2-23)** (0.20 g, 94%) as yellow crystals, m.p. 297-298°, identical (t.l.c., ^{1}H n.m.r., m.s.) with the material prepared above.

*2,4,7-Trichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (2,4,7-Trichloronorlichexanthone)* **(2-26)**

A solution of sulfuryl chloride (0.06 mmol) in anhydrous dioxane (1 ml) was added dropwise to a solution of 4,7-dichloro-8-methyl-1,3,6-trihydroxy-9*H*-xanthen-9-one **(2-23)** (20 mg, 0.06 mmol) in anhydrous dioxane (1 ml) and the mixture stirred at room temperature for 4.5 h. Evaporation of the solvent under reduced pressure then gave the crude product. This was purified by radial chromatography (SiO_2) using 30-100% ethyl acetate / light petroleum as eluant to give *2,4,7-trichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one* **(2-26)** (13 mg, 60%), m.p. 228-229° (Found: mol. wt. 359.9359. $C_{14}H_7O_5{}^{35}Cl_3$ requires: mol. wt. 359.9359). ^{1}H n.m.r. [$(CD_3)_2CO$] δ 2.92, 3H, s, Me; 6.96, 1H, s, H5; 8.92, 1H, s, OH. Mass spectrum *m/z* 366 (3.5%), 364 (30.6), 362 (93.9), 360 (M, 100.0), 330 (2.3), 328 (8.5), 326 (13.2). Standard

t.l.c. R_F values: R_F (A) 0.51; R_F (B) 0.50; R_F (C) 0.34; R_F (E) 0.04. Standard h.p.l.c. RI value: 0.89.

6.2.c. Synthesis of 3-Methoxy-8-methyl-9*H*-xanthen-9-ones

*6-Benzyloxy-4,7-dichloro-1,3-dihydroxy-8-methyl-9*H*-xanthen-9-one* **(2-24)**

A mixture of benzyl 6-benzyloxy-4,7-dichloro-1,3-dihydroxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylate **(2-18)** (0.4 g, 0.73 mmol), dimethyl sulfoxide (6 ml), potassium hydroxide (0.6 g) and water (4 ml) was stirred and heated in a nitrogen atmosphere at 120-135° for 1.5 h, and then poured into cold, dilute hydrochloric acid and the solid was filtered. The solid product was crystallized from dimethylformamide to give *6-benzyloxy-4,7-dichloro-1,3-dihydroxy-8-methyl-9*H*-xanthen-9-one* **(2-24)** (0.28 g, 92%) as yellow crystals, m.p. 272-274° (Found: mol.wt. 416.0218. $C_{21}H_{14}O_5{}^{35}Cl_2$ requires: mol. wt. 416.0218). ^{1}H n.m.r. [$(CD_3)_2CO$] δ 2.92, 3H, s, Me; 5.45, 2H, s, CH_2Ph; 6.43, 1H, s, H2; 7.26, 1H, s, H5; 7.47, 5H, m, Ph. Mass spectrum *m/z* 420 (0.3%), 418 (1.6), 416 (M, 2.4), 330 (0.2), 328 (1.4), 326 (2.2), 91 (100.0).

*6-Benzyloxy-4,7-dichloro-1-hydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one* **(2-25)**

A mixture of 6-benzyloxy-4,7-dichloro-1,3-dihydroxy-8-methyl-9*H*-xanthen-9-one **(2-24)** (0.48 g, 1.15 mmol), dimethyl sulfate (0.45 g, 3.6 mmol), potassium carbonate (0.9 g), acetone (25 ml) and dimethylformamide (10 ml) were stirred and refluxed for 20 h. The cooled reaction mixture was then poured into cold dilute hydrochloric acid and the precipitated product was filtered. The product was crystallized from dimethylformamide to give *6-benzyloxy-4,7-dichloro-1-hydroxy-3-methoxy-8-*

*methyl-9*H-*xanthen-9-one* (**2-25**) (0.35 g, 71%) as pale yellow crystals, m.p. 258-259° (Found: C, 61.4; H, 3.6, Cl, 16.7. $C_{22}H_{16}O_5Cl_2$ requires: C, 61.3; H, 3.7; Cl, 16.4%). ^{1}H n.m.r. [$(CD_3)_2CO$] δ 2.92, 3H, s, ArMe; 4.04, 3H, s, OMe; 5.49, 2H, s, CH_2Ph; 6.62, 1H, s, H2; 7.25, 1H, s, H5; 7.45, 5H, m, Ph. Mass spectrum *m/z* 434 (0.4%), 432 (2.4), 430 (M, 3.8), 91 (100.0).

*4,7-Dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H-*xanthen-9-one* (**2-27**)

A solution of 6-benzyloxy-4,7-dichloro-1-hydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one (**2-25**) (0.1 g, 0.23 mmol) in dry dichloromethane (20 ml) was cooled to -10°. Boron trichloride (1.4 mmol) in dichloromethane (1.4 ml) was then added slowly and the mixture was stirred at -10° for 1 h and then at room temperature for further 4 h. The mixture was then poured into ice-water, the dichloromethane removed on a rotary evaporator and the precipitate filtered and washed with water. The product was crystallized from ethyl acetate / cyclohexane to give 4,7-dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one (**2-27**) (70 mg, 89%) as yellow needles, m.p. 233-236° dec. (lit.[122] m.p. 246-247°) (Found: C, 52.7; H, 2.9; Cl, 20.4. $C_{15}H_{10}O_5Cl_2$ requires: C, 52.8; H, 3.0; Cl, 20.8%). ^{1}H n.m.r. ($CDCl_3$) δ 3.01, 3H, s, ArMe; 3.97, 3H, s, OMe; 6.40, 1H, s, H2; 7.05, 1H, s, H5; 8.15 and 13.30, each 1H, s, OH. Mass spectrum *m/z* 344 (11.0%), 342 (68.4), 340 (M, 100.0), 315 (0.8), 313 (5.4), 311 (8.8), 306 (3.3).

*2,4,7-Trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H-*xanthen-9-one* (**2-28**) *and 4,5,7-Trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H-*xanthen-9-one* (**2-29**)

A solution of 4,7-dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one (**2-27**) (0.102 g, 0.3 mmol), *N*-chlorosuccinimide (0.06 g, 0.45 mmol) and several

crystals of toluene - 4 - sulphonic acid in dimethylformamide (10 ml) was heated to 100° and stirred for 20 h. The solution was then poured into water and extracted with ethyl acetate. The combined organic extract was washed with water, brine and then dried ($MgSO_4$). The crude product obtained on evaporation of the solvent was purified by preparative thin layer chromatography (SiO_2) using 50% of ethyl acetate / light petroleum as eluant. The faster moving band yielded *2,4,7-trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H-*xanthen-9-one* **(2-28)** (20 mg, 18%) as yellow crystals, m.p. 257-259° dec. (Found: mol. wt. 373.9515. $C_{15}H_9O_5{}^{35}Cl_3$ requires: mol. wt. 373.9516). ^{1}H n.m.r. [$(CD_3)_2CO$] δ 2.95, 3H, s, ArMe; 4.02, 3H, s, OMe; 7.05, 1H, s, H5; 7.44 and 13.93, each 1H, s, OH. Mass spectrum *m/z* 380 (3.0%), 378 (20.9), 376 (73.0), 374 (M, 77.1), 335 (4.7), 333 (13.9), 331 (14.2), 91 (100.0).

The slower moving band contained the isomer, *4,5,7-trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H-*xanthen-9-one* **(2-29)** (10 mg, 9%) as yellow crystals, m.p. 285-287° dec. (Found: mol. wt. 373.9515. $C_{15}H_9O_5{}^{35}Cl_3$ requires: mol. wt. 373.9516). ^{1}H n.m.r. [$(CD_3)_2CO$] δ 2.93, 3H, s, ArMe; 4.02, 3H, s, OMe; 6.50, 1H, s, H2. Mass spectrum *m/z* 380 (3.8%), 378 (27.2), 376 (94.7), 374 (M, 100.0), 348 (2.4), 346 (5.8), 344 (5.4), 339 (3.1), 310 (9.7). Standard t.l.c. R_F values: R_F (A) 0.66; R_F (B) 0.64; R_F (C) 0.65; R_F (F) 0.32. Standard h.p.l.c. RI value: 1.75. The t.l.c. and h.p.l.c. behaviour of synthetic **(2-29)** was identical with that of one of the major metabolites of the lichen *Lecidella asema* Nyl.

6.3. Synthesis of Norlichexanthones via a Friedel-Crafts Approach

6.3.a. Synthesis of Isoarthothelin

Ethyl 3,5-Dichloro-2,4-dihydroxy-6-methylbenzoate **(3-15)**

A solution of ethyl orsellinate **(2-6)** (10 g, 0.051 mol) in anhydrous diethyl ether (200 ml) was treated with a solution of sulfuryl chloride (13.7 g, 0.102 mol) in anhydrous ether (100 ml) and stirred at 17° for 17 h. Evaporation of the solvent under reduced pressure gave the crude product which was crystallized from dichloromethane to give ethyl 3,5-dichloro-2,4-dihydroxy-6-methylbenzoate **(3-15)** (9.3 g, 69%) as colourless crystals, m. p. 160° (lit.[115] m.p. 160-163°).

Ethyl 2,4-Dibenzyloxy-3,5-dichloro-6-methylbenzoate **(3-16)**

A mixture of ethyl 3,5-dichloro-2,4-dihydroxy-6-methylbenzoate **(3-15)** (9.3 g, 35 mmol), benzyl bromide (12 g, 70.2 mmol), and potassium carbonate (24 g) in acetone (200 ml) was refluxed for 18 h. The mixture was then cooled and poured into cold diluted hydrochloric acid and extracted with ether. The ether layer was washed with water, brine and then dried ($MgSO_4$). The crude product was then purified by column chromatography over SiO_2 using 5%-15% ethyl acetate / light petroleum as eluant to give ethyl 2,4-dibenzoxyl-3,5-dichloro-6-methylbenzoate **(3-16)** (11.8 g, 76%) which crystallized from light petroleum in colourless plates, m.p. 77-78° (lit.[115] m.p. 77-78°).

2,4-Dibenzyloxy-3,5-dichloro-6-methylbenzoic Acid **(3-17)**

A mixture of ethyl 2,4-dibenzyloxy-3,5-dichloro-6-methylbenzoate **(3-16)** (14 g, 31.6 mmol), dimethyl sulfoxide (170 ml), potassium hydroxide (7.8 g) and water (30

ml) was stirred and heated at 98° for 4 h, then cooled and diluted with water. The basic aqueous layer was poured into cold dilute hydrochloric acid, extracted with ether and the ethereal extract washed with water, with saturated brine and then dried ($MgSO_4$). After removal of solvent the residue was crystallized from cyclohexane to give 2,4-dibenzyloxy-3,5-dichloro-6-methylbenzoic acid **(3-17)** (8.3 g, 63%) as a colourless fluffy crystals, m.p. 180-182° (lit.[115] m.p. 180-182°, lit.[119] 186-188°).

Benzyl 2,4,6-Tribenzyloxy-3-chlorobenzoate **(3-19)**

A solution of sulfuryl chloride (3.5 ml, 8% excess) in anhydrous ether (90 ml) was added dropwise at room temperature to a stirred solution of 2,4,6-trihydroxybenzoic acid **(2-10)** (6.8 g, 0.04 mol) in anhydrous ether (300 ml). After 2 h the solution was poured into ice and the ethereal layer washed with water, dried ($MgSO_4$) and evaporated to give 3-chloro-2,4,6-trihydroxybenzoic acid **(3-18)** (6.8 g, 83%) as colourless crystals. ^1H n.m.r. ($CDCl_3$) δ 6.21, 1H, s, ArH. Attempts to recrystallize the acid resulted in decarboxylation.

A mixture of 3-chloro-2,4,6-trihydroxybenzoic acid **(3-18)** prepared above (6.5 g, 0.032 mol), benzyl bromide (15 ml, 0.128 mol) and potassium carbonate (34 g) in acetone (200 ml) was stirred at room temperature for 36 h. The mixture was then poured into cold dilute hydrochloric acid and extracted with ether. The ether layer was washed with water and brine and then dried ($MgSO_4$). The crude product obtained on evaporation of the solvent was purified by column chromatography (SiO_2) using 5%-15% ethyl acetate / light petroleum as eluant to give benzyl 2,4,6-tribenzyloxy-3-chlorobenzoate **(3-19)** (9 g, 50%) which crystallized from the eluant as colourless crystals, m.p. 96-98° (lit.[122] m.p. 96-96.5°). ^1H n.m.r. ($CDCl_3$) δ 4.99, 5.05 and 5.09, each 2H, s, $ArOCH_2Ph$; 5.23, 2H, s, CO_2CH_2Ph; 6.38, 1H, s, ArH; 7.24-7.44,

20H, m, Ph (lit.[119] ^{1}H n.m.r. ($CDCl_3$) δ 4.91, 2H, s, $ArOCH_2Ph$; 5.05, 4H, s, $ArOCH_2Ph$; 5.21, 2H, s, CO_2CH_2Ph; 6.36, 1H, s, ArH; 7.2-7.6, 20H, m, Ph).

2,4,6-Tribenzyloxy-3-chlorobenzoic Acid (**3-20**)

A mixture of benzyl 2,4,6-tribenzyloxy-3-chlorobenzoate (**3-19**) (1.5 g, 2.65 mmol), dimethyl sulfoxide (36 ml), potassium hydroxide (3.6 g) and water (6 ml) was stirred and heated at 98° for 1.5 h, then diluted with water. The basic aqueous layer was poured into cold diluted hydrochloric acid, extracted with ether and the ethereal extract washed with water, with saturated brine and then dried ($MgSO_4$). After the removal of solvent the residue was crystallized from cyclohexane to give 2,4,6-tribenzyloxy-3-chlorobenzoic acid (**3-20**) (0.8 g, 61%) as colourless crystals, m.p. 133-135° (lit.[122] m.p. 133.5-134.5°). ^{1}H n.m.r. ($CDCl_3$) δ 5.06, 2H, s, CH_2Ph; 5.10, 4H, s, CH_2Ph; 6.40, 1H, s, ArH; 7.30-7.44, 15H, m, Ph.

1,3,5-Tribenzyloxy-2-chlorobenzene (**3-21**)

A mixture of 2,4,6-tribenzyloxy-3-chlorobenzoic acid (**3-20**) (2.1 g, 4.17 mmol), cuprous oxide (0.125 g) and 2,2'-bipyridyl (0.93 g) in anhydrous dimethylformamide (40 ml) was heated under gentle reflux in a nitrogen atmosphere for 2.5 h. The mixture was cooled and poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, brine and then dried ($MgSO_4$). After removal of solvent the crude product was purified by column chromatography (SiO_2) using 3-7% ethyl acetate / light petroleum as eluant to give *1,3,5-tribenzyloxy-2-chlorobenzene* (**3-21**) (1.2 g, 67 %) as colourless needles, m.p. 69-70° (Found: C,75.0; H, 5.5; Cl, 8.3. $C_{27}H_{23}O_3Cl$ requires: C, 75.3; H, 5.4; Cl, 8.2%). ^{1}H n.m.r. ($CDCl_3$) δ 4.94, 2H, s, CH_2Ph; 5.09, 4H, s, CH_2Ph; 6.29, 2H, s, ArH;

7.35-7.39, 15H, m, Ph. Mass spectrum *m/z* 432 (0.7%), 430 (M, 2.2), 182 (0.8), 180 (4.0), 91 (100).

2',4,4',6'-Tetrabenzyloxy-3,3',5-trichloro-2-hydroxy-6-methylbenzophenone **(3-22)**

A solution of trifluoroacetic anhydride (0.58 ml) in 1,2-dichloroethane (0.58 ml) was added to a stirred solution of 2,4-dibenzyloxy-3,5-dichloro-6-methybenzoic acid (**3-17**) (0.146 g, 0.35 mmol) in 1,2-dichloroethane (2.9 ml) at 0°. After 20 min a solution of 1,3,5-tribenzyloxy-2-chlorobenzene (**3-21**) (0.65 g, 1.51 mmol) in 1,2-dichloroethane (5.8 ml) was added at 0° and the solution was then refluxed for 8 days. The cooled solution was washed several times with 1% ammonium hydroxide solution, then with water and finally with saturated brine. After drying ($MgSO_4$) the solvent was evaporated and the mixture was separated by radial chromatography (SiO_2) using 4% ethyl acetate / light petroleum as eluant to give *2',4,4',6'-tetrabenzyloxy-3,3',5-trichloro-2-hydroxy-6-methylbenzophenone* (**3-22**) (60 mg, 21%) as yellow crystals, m.p. 114-115° (Found: C, 68.6; H, 4.7; Cl, 13.9. $C_{42}H_{33}O_6Cl_3$ requires: C, 68.2; H, 4.5; Cl, 14.4%). ^1H n.m.r. ($CDCl_3$) δ 2.11, 3H, s, Me; 4.59, 2H, s, CH_2Ph; 4.83, 4H, s, CH_2Ph; 5.16, 2H, s, CH_2Ph; 6.01, 1H, s, ArH; 7.24-7.38, 20H, m, Ph; 13.87, H, s, OH. Mass spectrum *m/z* 631 (1.0%), 430 (0.5), 181 (2.9), 91 (100.0).

*2,5,7-Trichloro-1,3,6-trihydrouxy-8-methyl-9*H*-xanthen-9-one (Isoarthothelin)* **(1-29)**

A solution of boron trichloride (0.4 mmol) in dichloromethane (0.4 ml) was added to a solution of the foregoing benzophenone (**3-22**) (35 mg, 0.042 mmol) in dichloromethane (3 ml) at -10°. The mixture was stirred at -10° for 0.5 h and then at room temperature for 3.5 h. The mixture was then diluted with water and the solvent was evaporated. The residue was extracted with ethyl acetate and the extract washed

with water, brine and then dried ($MgSO_4$). The residue obtained on evaporation of the solvent was purified by radial chromatography (SiO_2) using 50% ethyl acetate / light petroleum as eluant and then the main band was further purified by preparative t.l.c. (SiO_2) using ethyl acetate as eluent to give *3,3',5'-trichloro-2,2',4,4',6'-pentahydroxy-6-methylbenzophenone* (**3-23**) (10 mg, 63 %) as yellow crystals. ^1H n.m.r. [$(CD_3)_2CO$] δ 2.17, 3H, s, Me; 6.11, 1H, s, ArH. Mass spectrum *m/z* 366 (5.2%), 364 (24.7), 362 (70.2), 360 (74.4), 223 (6.3), 221 (30.2), 219 (46.6), 191 (10.6), 189 (32.1), 187 (92.1), 69 (100.0).

A solution of the above 3,3',5'-trichloro-2,2',4,4',6'-pentahydroxy-6-methylbenzophenone (**3-23**) (13.7 mg, 0.036mml) in 1% ethanolic potassium hydroxide (2 ml) was refluxed in a nitrogen atmosphere for 1.5 h. The cooled mixture was poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, brine and dried ($MgSO_4$). After removal of the solvent the mixture was purified by preparative t.l.c. (SiO_2) using ethyl acetate as eluant to give 2,5,7-trichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one (isoarthothelin) (**1-29**) (6 mg, 45%) which crystallized from acetone as a yellow needles, m.p. 253-254° (lit.[108] m.p. 247-248°; lit.[119] m.p. 250-251°) (Found: mol. wt. 359.9359. $C_{14}H_7O_5{}^{35}Cl_3$ requires: mol.wt. 359.9359). ^1H n.m.r. [$(CD_3)_2SO$] δ 3.00, 3H, s, ArMe; 6.41, 1H, s, H4. Mass spectrum *m/z* 364 (1.7%), 362 (5.9), 360 (M, 6.4), 181 (2.3), 149 (9.6), 91 (15.3), 43 (100.0). Standard t.l.c.[44] R_F values: R_F (A) 0.45; R_F (B) 0.44; R_F (C) 0.36; R_F (E) 0.06. Standard h.p.l.c.[44] RI values: 0.81. This sample was found to be identical (t.l.c., h.p.l.c., ^1H n.m.r., m.s.) with the natural xanthone isolated[34,97] from an Australian *Buellia* sp.

6.3.b. Extraction and Degradation of Xanthones from *Lecanora broccha*

Extraction of the Lichen Lecanora broccha

The air-dried lichen thallus (66 g) was separated from adhering soil and grass and extracted (Soxhlet extractor) for 24 h with anhydrous ether (1 litre) and then for a further 24 h with acetone (1 litre). The combined solvents were removed to give a mixture of xanthones (0.7 g) which were purified by preparative t.l.c. (SiO_2) using ethyl acetate as eluant. The faster moving band yielded *5,7-dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one* **(3-25)** (51 mg) as pale yellow crystals, m.p. 248-250° (Found: mol. wt. 339.9902. $C_{15}H_{10}O_5{}^{35}Cl_2$ requires: mol. wt. 339.9905). ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2.82, 3H, s, ArMe; 3.85, 3H, s, OMe; 6.24, 1H, d, *J* 2Hz, H2; 6.43, 1H, d, *J* 2Hz, H4; 14.00, 1H, s, OH. Mass spectrum *m/z* 344 (15.6%), 342 (73.0), 340 (M, 100.0), 315 (4.0), 313 (15.6), 311 (24.7), 91 (43.1). Standard t.l.c. R_F values: R_F (A) 0.67; R_F (B) 0.67; R_F (C) 0.59; R_F (F) 0.40. Standard h.p.l.c. RI value: 1.15.

The slower band yielded 2,5,7-trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthene-9-one **(3-24)** (180 mg) as pale yellow crystals, m.p. 259-261° (lit.[119] 259-261°) (Found: mol. wt. 373.9518. $C_{15}H_9O_5{}^{35}Cl_3$ requires: mol. wt. 373.9516). ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2.91, 3H, s, ArMe; 4.05, 3H, s, OMe; 6.81, 1H, s, H4; 7.73 and 13.82, each 1H, s, OH. Mass spectrum *m/z* 378 (4.9%), 376 (18.8), 374 (M, 19.1), 97 (20.2), 91 (29.5), 44 (100.0). Standard t.l.c. R_F values: R_F (A) 0.64; R_F (B) 0.56; R_F (C) 0.56; R_F (E) 0.06. Standard h.p.l.c.[129] RI value: 1.29.

*Demethylation of Natural 5,7-Dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one* **(3-25)**

Boron tribromide (2 ml) was added to a solution of 5,7-dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one **(3-25)** (25 mg, 0.07 mmol) in dichloromethane (5 ml) at -10°. The mixture was stirred at -10° for 0.5 h and then at room temperature for 48 h. The mixture was then diluted with water and the solvent was evaporated. Then the residue was extracted with ethyl acetate and the extract was washed with water, brine and then dried ($MgSO_4$). The residue obtained on removal of the solvent was purified by preparative t.l.c. (SiO_2) using 50% ethyl acetate / light petroleum as eluant. The major band afforded 5,7-dichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-9-one **(3-26)** (10 mg, 45%) which crystallized from the eluant as pale yellow crystals, identical with the authentic material[37] (h.p.l.c., t.l.c.). ^{1}H n.m.r. [$(CD_3)_2CO$] δ 2.98, 3H, s, ArMe; 6.20, 1H, d, *J* 2.1 Hz, H2; 6.40, 1H, d, *J* 2.1 Hz, H4; 13.62, 1H, s, OH. Standard t.l.c. R_F values: R_F (A) 0.44; R_F (B) 0.48; R_F (C) 0.33; R_F (F) 0.43. Standard h.p.l.c. RI value: 0.60.

*Demethylation of Natural 2,5,7-Trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthene-9-one* **(3-24)**

Boron tribromide (2 ml) was added to a solution of 2,5,7-trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthene-9-one **(3-24)** (7 mg, 0.019 mmol) in dichloromethane (3 ml) at -10°. The mixture was stirred at -10° for 0.5 h and then at room temperature for 48 h. The mixture was then diluted with water and the solvent was evaporated. Then the residue was extracted with ethyl acetate and the extract was washed with water, brine and dried ($MgSO_4$). The residue obtained on removal of the solvent was purified by preparative t.l.c. (SiO_2) using 50% ethyl acetate / light petroleum as eluant. The major band afforded 2,5,7-trichloro-1,3,6-trihydroxy-8-methyl-9*H*-xanthen-

9-one (isoarthothelin) **(1-29)** (4 mg, 65%) which crystallized from acetone as pale yellow needles, m.p. 253-254° (lit.[108] m.p. 247-248°; lit.[119] m.p. 250-251°), identical with the synthetic material (h.p.l.c., t.l.c., ^{1}H n.m.r., m.s.).

6.3.c. Synthesis of Xanthones from *Lecanora broccha*

1,3,5-Trimethoxybenzene **(3-28)**

A mixture of anhydrous phloroglucinol **(3-27)** (4.1 g, 33 mmol), dimethyl sulfate (9.2 ml, 98 mmol) and anhydrous potassium carbonate (33 g) in acetone (230 ml) was stirred and refluxed for 24 h. The cool reaction mixture was then poured into cold diluted hydrochloric acid and extracted with ether. The ether extract was washed with water, saturated brine and then dried ($MgSO_4$). The solvent was evaporated and the residue was separated by flash chromatography (SiO_2) using 13% ethyl acetate / light petroleum as eluant to give 1,3,5-trimethoxybenzene **(3-28)** (3.1 g, 56 %) which crystallized from the eluant as colourless crystals, m.p. 48-49° (lit.[56] m.p. 54-55°) (Found: C, 64.6; H, 7.4. $C_9H_{12}O_3$ requires: C, 64.3; H, 7.2%). ^{1}H n.m.r. ($CDCl_3$) δ 3.76, 9H, s, OMe; 6.08, 3H, s, ArH. Mass spectrum *m/z* 168 (M, 100.0%), 139 (84.2), 125 (19.7).

3,5-Dimethoxyphenol **(3-29)**

Anhydrous phloroglucinol **(3-27)** (50 g, 0.4 mol) was dissolved in dry acetone-free methanol (300 ml) and a stream of dry hydrogen chloride passed through the solution during 1 h at such a rate as to raise the temperature of the solvent to boiling point. The solution was then refluxed for 1 h, re-saturated with hydrogen chloride for a further 1 h, and then stood overnight. The greater part of the methanol was then

evaporated under reduced pressure and the heavy oil that separated on the addition of water, was dissolved in ether. The ethereal solution was washed with water, dried ($MgSO_4$), concentrated and the residue distilled. The product **(3-29)** (39 g, 65 %) was obtained as a pale yellow oil, b.p. 139-141° / 0.5 mm (lit.[98] b.p. 185-190° / 20 mm). ^1H n.m.r. ($CDCl_3$) δ 3.74, 6H, s, OMe; 5.22, 1H, s, OH; 6.03, 3H, s, ArH.

4-Chloro-3,5-dimethoxyphenol **(3-30)** *and 2-Chloro-3,5-dimethoxyphenol* **(3-31)**

A solution of 3,5-dimethoxyphenol **(3-29)** (5.45 g, 35 mmol) in anhydrous ether (50 ml) was treated with a solution of sulfuryl chloride (2.87 ml, 35 mmol) in anhydrous ether (15 ml) and stirred at 20° for 24 h. After removal of solvent the residue was purified by flash chromatography (SiO_2) using 15 % ethyl acetate / light petroleum as eluant. The faster moving band afforded 2-chloro-3,5-dimethoxyphenol **(3-31)** (3.3 g, 50%) as colourless crystals, m.p. 59-60° (lit.[57] m.p. 60-61°). ^1H n.m.r. ($CDCl_3$) δ 3.77 and 3.85, each 3H, s, OMe; 5.72, 1H, s, OH; 6.12, 1H, d, *J* 2 Hz, H4; 6.24, 1H, d, *J* 2Hz, H6. Mass spectrum *m/z* 190 (31.0%), 188 (M, 100.0), 159 (21.0), 145 (37.1).

The slower moving fractions were concentrated and the residue crystallized from cyclohexane / dichloromethane to give 4-chloro-3,5-dimethoxyphenol **(3-30)** (2.2 g, 33%) as colourless prisms, m.p. 132-134° (lit.[57] m.p. 132-133°). ^1H n.m.r. ($CDCl_3$) δ 3.85, 6H, s, OMe; 6.12, 2H, s, ArH. Mass spectrum *m/z* 190 (31.5%), 188 (M, 100.0), 159 (21.9), 154 (14.4).

5-Benzyloxy-2-chloro-1,3-dimethoxybenzene **(3-32)**

A mixture of 4-chloro-3,5-dimethoxyphenol **(3-30)** (2 g, 10.6 mmol), benzyl bromide (1.26 ml, 10.6 mmol), and potassium carbonate (3.7 g) in acetone (20 ml) was refluxed for 30 h. The mixture was then cooled and poured into cold dilute hydrochloric acid and extracted with ether. The ether layer was washed with water and brine and then dried ($MgSO_4$). The crude product obtained on evaporation of the solvent was then crystallized from cyclohexane to give 5-benzyloxy-2-chloro-1,3-dimethoxybenzene **(3-32)** (2.2 g, 75%) as colourless crystals, m.p. 84-85° (lit.[57] m.p. 97-98°). ^1H n.m.r. ($CDCl_3$) δ 3.82, 6H, s, OMe; 5.05, 2H, s, CH_2Ph; 6.26, 2H, s, ArH; 7.40, 5H, m, Ph. Mass spectrum *m/z* 280 (0.7%), 278 (M, 2.2), 91 (100.0).

2,4-Dibenzyloxy-3,5-dichloro-2',4',6'-trimethoxy-6-methyl-3'-trifluoroacetylbenzophenone **(3-33)**

A solution of trifluoroacetic anhydride (4 ml) in 1,2-dichloroethane (4 ml) was added to a stirred solution of 2,4-dibenzyloxy-3,5-dichloro-6-methybenzoic acid **(3-17)** (0.61 g, 1.46 mmol) in 1,2-dichloroethane (15 ml) at 0°. After 20 min a solution of 1,3,5-trimethoxybenzene **(3-28)** (1.0 g, 6.03 mmol) in 1,2-dichloroethane (20 ml) was added at 0° and then the solution was refluxed for 8 days. The cooled solution was washed with 1% ammonium hydroxide solution, with water and finally with saturated brine. The residue obtained on evaporation of the solvent was purified by radial chromatography (SiO_2) using 4-20% ethyl acetate / light petroleum as eluant to give *2,4-dibenzyloxy-3,5-dichloro-2',4',6'-trimethoxy-6-methyl-3'-trifluoroacetylbenzophenone* **(3-33)** (0.44 g, 46%) as colourless crystals, m.p. 30-34° (Found: C, 59.3; H, 4.5; Cl, 10.2; F, 7.7. $C_{33}H_{27}O_7Cl_2F_3$ requires: C, 59.7; H, 4.1; Cl, 10.7; F, 8.6%). ^1H n.m.r. ($CDCl_3$) δ 2.35, 3H, s, ArMe; 3.52, 3.62 and 3.82, each 3H, s, OMe; 4.80 and 5.08,

each 2H, s, CH_2Ph; 6.08, 1H, s, ArH; 7.33-7.41, 10H, m, Ph. Mass spectrum *m/z* 662 (M, 0.3%), 616 (1.4), 593 (0.2), 354 (2.4), 291 (1.9), 149 (2.3), 91 (100.0).

*5,7-Dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one* (**3-25**)

A solution of boron trichloride (20 mmol) in 20 ml dichloromethane was added slowly to a solution of the foregoing benzophenone (**3-33**) (1.2 g, 2 mmol) in dichloromethane (20 ml) at -10°. The resulting mixture was stirred at 10° for 1 h and then at room temperature for 4 h. The mixture was then diluted with water and the solvent was evaporated. The residue obtained was extracted with ethyl acetate and the extract was washed with water, brine and dried ($MgSO_4$). The residue obtained on evaporation of the solvent was purified by radial chromatography (SiO_2) using 50% ethyl acetate / light petroleum as eluant and then by preparative t.l.c. (SiO_2) using ethyl acetate as eluant to give *3,5-dichloro-2,2',4,6'-tetrahydroxy-4'-methoxy-6-methyl-3'-trifluoroacetylbenzophenone* (**3-34**) (0.56 g, 62%) as pale yellow crystals, m.p. 130° dec. ^{1}H n.m.r. ($CDCl_3$) δ 2.17, 3H, s, ArMe; 3.82, 3H, s, OMe; 6.34, 1H, s, ArH; 13.37, 1H, s, OH. Mass spectrum *m/z* 438 (2.9%), 436 (4.6), 367 (24.7), 149 (13.6), 113 (4.4), 91 (15.5), 44 (100.0).

A solution of the above 3,5-dichloro-2,2',4,6'-tetrahydroxy-4'-methoxy-6-methyl-3'-trifluoroacetylbenzophenone (**3-34**) (60 mg, 0.17 mmol) in 1% ethanolic potassium hydroxide (5 ml) was refluxed in an atmosphere of nitrogen for 0.5 h. The cooled mixture was then poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine and then dried ($MgSO_4$). The mixture was purified by preparative t.l.c. (SiO_2) using 50% ethyl acetate / light petroleum as eluant to give *5,7-dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one* (**3-25**) (27 mg, 47%) which crystallized from the eluant as yellow crystals, softening at 164-166° and m.p. 248-250°. This synthetic sample was found to

be identical (t.l.c., h.p.l.c., ^1H n.m.r., m.s.) with the natural xanthone isolated from *Lecanora broccha.*

2,4,6'-Tribenzyloxy-3,3',5-trichloro-2',4'-dimethoxy-6-methylbenzophenone **(3-35)**

A solution of trifluoroacetic anhydride (2 ml) in 1,2-dichloroethane (4 ml) was added to a stirred solution of 2,4-dibenzyloxy-3,5-dichloro-6-methybenzoic acid **(3-17)** (0.62 g, 1.5 mmol) and 5-benzyloxy-2-chloro-1,3-dimethoxybenzene **(3-32)** (1.18 g, 4.2 mmol) in 1,2-dichloroethane (34 ml) at 0°. After being stirred for a further 20 min the solution was refluxed for 3 days. Then further trifluoroacetic anhydride (2 ml) was added and the mixture was refluxed for a further 4 days. The cooled solution was washed with 1% ammonium hydroxide solution, with water, brine and then dried ($MgSO_4$). The residue obtained on evaporation of the solvent was separated by radial chromatography (SiO_2) using 10% ethyl acetate / light petroleum to give 2,4,6'-tribenzyloxy-3,3',5-trichloro-2',4'-dimethoxy-6-methylbenzophenone **(3-35)** (0.9 g, 90%) as yellow prisms, m.p. 134-137° (lit.[109] m.p. 137-141°). ^1H n.m.r. ($CDCl_3$) δ 2.18, 3H, s, ArMe; 3.80 and 3.85, each 3H, s, OMe; 4.74, 4.89 and 5.08, each 2H, s, CH_2Ph; 6.26, 1H, s, ArH; 7.39, 15H, m, Ph.

3,3',5-Trichloro-2,2',4,6'-tetrahydroxy-4'-methoxy-6-methylbenzophenone **(3-36)**

Boron tribromide (1.2 ml, 12 mmol) was added to a solution of 2,4,6'-tribenzyloxy-3,3',5-trichloro-2',4'-dimethoxy-6-methylbenzophenone **(3-35)** (0.51 g, 1.25 mmol) in dichloromethane (5 ml) at 0°. The mixture was stirred at 0° for 0.5 h and then at room temperature for 5 h. The mixture was then diluted with water and the solvent was evaporated. The residue was extracted with ethyl acetate and the extract was washed with water, brine and then dried ($MgSO_4$). The residue left after removal of the

solvent was separated by radial chromatography (SiO_2) using 40-60% ethyl acetate / light petroleum as eluant. The major band yielded 3,3',5-trichloro-2,2',4,6'-tetrahydroxy-4'-methoxy-6-methylbenzophenone **(3-36)** (55 mg, 11%) which was further purified by preparative t.l.c. (SiO_2) using 50% ethyl acetate / light petroleum as eluent and crystallized from this solvent to form pale yellow crystals, m.p. 135-137° (lit.[119] m.p. 127-140°). ^1H n.m.r. ($CDCl_3$) δ 2.22, 3H, s, ArMe; 3.94, 3H, s, OMe; 6.20, 1H, s, ArH; 12.7, 1H, s, OH. Mass spectrum *m/z* 380 (3.7%), 378 (30.1), 376 (92.2), 374 (M, 100.0), 310 (7.9), 113 (13.6), 111 (13.7), 103 (11.8), 91 (47.7).

*2,5,7-Trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one* **(3-24)**

A solution of 3,3',5-trichloro-2,2',4,6'-tetrahydroxy-4'-methoxy-6-methylbenzophenone **(3-36)** (25 mg, 0.064 mmol) in water (20 ml) was refluxed in an atmosphere of nitrogen for 18 h. The cooled mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine and then dried ($MgSO_4$). The residue obtained on removal of the solvent was purified by preparative t.l.c. (SiO_2) using ethyl acetate as eluant. The major band afforded 2,5,7-trichloro-3-methoxy-8-methyl-9*H*-xanthen-9-one **(3-24)** (17 mg, 71%) which crystallized from ethyl acetate as crystals, m.p. 259-261° (lit.[119] m.p. 259-261°). This synthetic sample was found to be identical (t.l.c., h.p.l.c., ^1H n.m.r., m.s.) with the natural xanthone isolated from *Lecanora broccha.*

6.3.d. Methylation of Natural Xanthones from *Lecanora broccha*

*5,7-Dichloro-1,3,6-trimethoxy-8-methyl-9*H*-xanthen-9-one* **(3-39)**

A mixture of 5,7-dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one **(3-25)** (100 mg, 0.29 mmol), dimethyl sulfate (0.07 ml, 0.74 mmol) and potassium carbonate (120 mg, 0.87 mmol) in dry acetone (10 ml) was refluxed for 16 h. The cooled mixture was poured into a mixture of ice and concentrated hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was purified by preparative t.l.c. (SiO_2) using 25% ethyl acetate / light petroleum as eluant. The major band yielded *5,7-dichloro-1,3,6-trimethoxy-8-methyl-9*H*-xanthen-9-one* **(3-39)** (50 mg, 47%) as yellow gum (Found: mol. wt. 368.0219. $C_{17}H_{14}O_5{}^{35}Cl_2$ requires: mol. wt. 368.0218). ^{1}H n.m.r. ($CDCl_3$) δ 2.85, 3H, s, ArMe; 3.92, 4.00 and 4.02, each 3H, s, OMe; 6.83, 1H, d, *J* 2.3Hz, H2; 6.90, 1H, d, *J* 2.3Hz, H4. Mass spectrum *m/z* 370 (1.5%), 368 (M, 2.2), 352 (3.7), 350 (6.6), 149 (27.3), 57 (100.0).

*5,7-Dichloro-1-hydroxy-3,6-dimethoxy-8-methyl-9*H*-xanthen-9-one* **(3-37)**

A solution of boron trichloride (1 mmol) in dichloromethane (1 ml) was added to a stirred solution of 5,7-dichloro-1,3,6-trimethoxy-8-methyl-9*H*-xanthen-9-one **(3-39)** (50 mg, 0.14 mmol) in anhydrous dichloromethane (5 ml) at room temperatue and the mixture was stirred for 4 h. The solvent was then removed and the residue dissolved in ethyl acetate. The organic extract was washed with water, brine and then dried ($MgSO_4$). After the removal of the solvent the crude product was purified by preparative t.l.c. (SiO_2) using 16% ethyl acetate / light petroleum as eluant. The major band afforded *5,7-dichloro-1-hydroxy-3,6-dimethoxy-8-methyl-9*H*-xanthen-9-one* **(3-37)** (20 mg, 40%) as pale yellow crystals, m.p. 135-138° (Found: mol. wt. 354.0061.

$C_{16}H_{12}O_5{}^{35}Cl_2$ requires: mol. wt. 354.0062). ^1H n.m.r. ($CDCl_3$) δ 3.01, 3H, s, ArMe; 3.90 and 4.01, each 3H, s, OMe; 6.36, 1H, d, *J* 2.3Hz, H2; 6.49, 1H, d, *J* 2.4Hz, H4; 12.95, 1H, s, OH. Mass spectrum *m/z* 358 (11.5%), 356 (69.1), 354 (M, 100.0), 329 (1.9), 327 (10.9), 325 (18.2). Standard t.l.c. R_F values: R_F (A) 0.47; R_F (B) 0.51; R_F (C) 0.32; R_F (E) 0.13; R_F (F) 0.52. Standard h.p.l.c. RI value: 3.06. The t.l.c. and h.p.l.c. behaviour of synthetic **(3-37)** was identical with that of one of the minor metabolites of the lichen *Lecanora broccha*.

*2,5,7-Trichloro-1,3,6-trimethoxy-8-methyl-9*H*-xanthen-9-one* **(3-40)**

A mixture of 2,5,7-trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one **(3-24)** (16 mg, 0.043 mmol), dimethyl sulfate (0.08 ml, 0.08 mmol) and potassium carbonate (25 mg, 0.18 mmol) in dry acetone (10 ml) was refluxed for 16 h. The cooled mixture was poured into a mixture of ice and concentrated hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was purified by preparative t.l.c. (SiO_2) using 25% ethyl acetate / light petroleum as eluant. The major band afforded *2,5,7-trichloro-1,3,6-trimethoxy-8-methyl-9*H*-xanthen-9-one* **(3-40)** (10 mg, 58%) which crystallized from the eluant as yellow crystals, m.p. 193-194° (Found: mol. wt. 401.9827. $C_{17}H_{13}O_5{}^{35}Cl_3$ requires: mol. wt. 401.9828). ^1H n.m.r. ($CDCl_3$) δ 2.98, 3H, s, ArMe; 4.00, 4.03 and 4.04, each 3H, s, OMe; 6.83, 1H, s, H4. Mass spectrum *m/z* 406 (13.0%), 404 (34.9), 402 (M, 35.9), 388 (57.7), 386 (93.9), 384 (100.0).

*2,5,7-Trichloro-1-hydroxy-3,6-dimethoxy-8-methyl-9*H*-xanthen-9-one* **(3-38)**

A solution of boron trichloride (0.15 mmol) in dichloromethane (0.15 ml) was added to a solution of 2,5,7-trichloro-1,3,6-trimethoxy-8-methyl-9*H*-xanthen-9-one **(3-40)** (10 mg, 0.025 mmol) in dry dichloromethane (3 ml) at room temperatue and the mixture was stirred for 5 h. The solvent was then removed and the residue dissolved in ethyl acetate. The ethyl acetate extract was washed with water, brine and then dried ($MgSO_4$). After the removal of the solvent the crude product was separated by preparative t.l.c. (SiO_2) using 25% ethyl acetate / light petroleum as eluant. The major band afforded *2,5,7-trichloro-1-hydroxy-3,6-dimethoxy-8-methyl-9*H*-xanthen-9-one* **(3-38)** (8 mg, 82%) which crystallized from ethyl acetate as pale yellow crystals, m.p. 197-199° (Found: mol. wt. 387.9670. $C_{16}H_{11}O_5{}^{35}Cl_3$ requires: mol. wt. 387.9672). ^{1}H n.m.r. ($CDCl_3$) δ 3.02, 3H, s, ArMe; 4.03 and 4.05, each 3H, s, OMe; 6.60, 1H, s, H4, 13.51, 1H, s, OH. Mass spectrum *m/z* 392 (0.7%), 390 (2.1), 388 (M, 2.4), 353 (2.3), 279 (2.1), 251 (3.7), 57 (100.0). Standard t.l.c. R_F values: R_F (A) 0.87; R_F (B) 0.74; R_F (C) 0.85; R_F (E) 0.58; R_F (F) 0.90. Standard h.p.l.c. RI value: 2.35. The t.l.c. and h.p.l.c. behaviour of synthetic **(3-38)** was identical with that of one of the minor metabolites of the lichen *Lecanora broccha*.

*Demethylation of 2,5,7-Trichloro-1-hydroxy-3,6-dimethoxy-8-methyl-9*H*-xanthen-9-one* **(3-38)** *Using Sodium Iodide*

A solution of 2,5,7-trichloro-1-hydroxy-3,6-dimethoxy-8-methyl-9*H*-xanthen-9-one **(3-38)** (10 mg, 0.026 mmol) in anhydrous dimethyl sulfoxide (2 ml) containing anhydrous sodium iodide[#] (30 mg, 0.2 mmol) was stirred and heated under reflux for 1.5 h in an atmosphere of dry nitrogen. The cooled mixture was poured into cold

[#] Dried at 30° in vacuum for 12 h.

hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, brine and then dried ($MgSO_4$). The residue obtained on removal of the solvent was purified by preparative t.l.c. (SiO_2) using 16% ethyl acetate / light petroleum as eluant. The major band afforded 2,5,7-trichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one **(3-24)** (8 mg, 82%) identical with the authentic compound (t.l.c., ^1H n.m.r.).

6.4. Synthesis of Two New Xanthones from a *Dimelaena* Lichen

6.4.a. Synthesis of 2,5-Dichloro-3-*O*-methylnorlichexanthone

Ethyl 2,4-Dibenzyloxy-3-chloro-6-methylbenzoate **(4-11)**

A mixture of ethyl 3-chloro-2,4-dihydroxy-6-methylbenzoate[56] **(4-10)** (9 g, 39 mmol), benzyl bromide (10.2 ml, 86 mmol) and potassium carbonate (16 g, 117 mmol) in anhydrous acetone (100 ml) was refluxed for 20 h. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ether. The ether extract was washed with water, brine and dried ($MgSO_4$). After removal of the solvent the crude product was purified by column chromatography (SiO_2) using 4-16% ethyl acetate / light petroleum as eluant. The major band afforded *ethyl 2,4-dibenzyloxy-3-chloro-6-methylbenzoate* **(4-11)** (9.1 g, 57%) as yellow oil (Found: mol. wt. 410.1286. $C_{24}H_{23}O_4{}^{35}Cl$ requires: mol. wt. 410.1285). ^1H n.m.r. ($CDCl_3$) δ 1.27, 3H, t, *J* 7Hz, $OCH_2\mathbf{CH_3}$; 2.31, 3H, s, ArMe; 4.29, 2H, q, *J* 7Hz, $O\mathbf{CH_2}CH_3$; 5.09 and 5.17, each 2H, s, CH_2Ph; 6.64, 1H, s, ArH; 7.34-7.50, 10H, m, Ph. Mass spectrum *m/z* 412 (0.2%), 410 (M, 0.4), 182 (2.8), 181 (17.5), 91 (100.0).

2,4-Dibenzyloxy-3-chloro-6-methylbenzoic Acid **(4-12)**

A mixture of ethyl 2,4-dibenzyloxy-3-chloro-6-methylbenzoate **(4-11)** (8.4 g, 20 mmol), potassium hydroxide (4.6 g), water (30 ml), and dimethyl sulfoxide (100 ml) was stirred at 90-95° for 2.5 h in an atmosphere of nitrogen. The cooled mixture was poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ethyl acetate. The organic extract was washed with water, brine and dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was crystallized from cyclohexane / ethyl acetate to give 2,4-dibenzyloxy-3-chloro-6-methylbenzoic acid **(4-12)** (6.7 g, 88%) as colourless needles, m.p. 140-141° (lit.[53] m.p. 142-143°). ^1H n.m.r. ($CDCl_3$) δ 2.48, 3H, s, ArMe; 5.12 and 5.21, each 2H, s, CH_2Ph; 6.71, 1H, s, ArH; 7.35-7.54, 10H, m, Ph. Mass spectrum *m/z* 382 (M, 0.1%), 181 (0.4), 91 (100.0).

2,4,6'-Tribenzyloxy-3,3'-dichloro-2',4'-dimethoxy-6-methylbenzophenone **(4-13)**

Trifluoroacetic anhydride (7 ml) was added to a stirred solution of 2,4-dibenzyloxy-3-chloro-6-methylbenzoic acid **(4-12)** (1.4 g, 3.7 mmol) and 5-benzyloxy-2-chloro-1,3-dimethoxybenzene **(3-32)** (1.36 g, 4.9 mmol) in anhydrous dichloromethane (35 ml) at 0°. The mixture was then stirred at room temperature for 7 h and was diluted with ethyl acetate. The solution was washed with saturated aqueous potassium hydrogen carbonate solution, water and saturated brine. After drying ($MgSO_4$) the solvent was evaporated and the crude product was separated by radial chromatography (SiO_2) using 15-50% ethyl acetate / light petroleum as eluant. The major band gave 2,4,6'-tribenzyloxy-3,3'-dichloro-2',4'-dimethoxy-6-methylbenzophenone **(4-13)** (0.8 g, 34%) as pale yellow crystals, m.p. 155-158° (lit.[53] m.p. 161-162°). ^1H n.m.r. ($CDCl_3$) δ 2.21, 3H, s, ArMe; 3.79 and 3.82, each 3H, s,

OMe; 4.70, 4.73 and 5.12, each 2H, s, CH_2Ph; 6.20 and 6.49, each 1H, s, ArH; 7.18-7.45, 15H, m, Ph. Mass spectrum *m/z* 607 (0.1%), 354 (0.2), 278 (0.5), 181 (2.0), 91 (100).

3,3'-Dichloro-2,2',4,6'-tetrahydroxy-4'-methoxy-6-methylbenzophenone **(4-14)**

Boron tribromide (1 ml, 10 mmol) was added to a stirred solution of 2,4,6'-tribenzyloxy-3,3'-dichloro-2',4'-dimethoxy-6-methylbenzophenone **(4-13)** (0.6 g, 1.02 mmol) in anhydrous dichloromethane (15 ml) at 0°. The mixture was then stirred at room tempertature for 6 h. Water was then added and the mixture was diluted with ethyl acetate. The organic layer was washed with water, brine and then dried ($MgSO_4$). After the removal of the solvent the crude product was purified by radial chromatography (SiO_2) using 20-80% ethyl acetate / light petroleum as eluant. The major band afforded 3,3'-dichloro-2,2',4,6'-tetrahydroxy-4'-methoxy-6-methylbenzophenone **(4-14)** (0.15 g, 42%) as pale yellow crystals, m.p. 118-123° (lit.[119] m.p. *ca* 123-135° dehydrat.) (Found: mol. wt. 358.0012. $C_{15}H_{12}O_6{}^{35}Cl_2$ requires: mol. wt. 358.0011). ^1H n.m.r. $[(CD_3)_2CO]$ δ 2.09, 3H, s, ArMe; 3.87, 3H, s, OMe; 6.13 and 6.43, each 1H, s, ArH; 7.14 and 11.87, each 1H, s, OH. Mass spectrum *m/z* 360 (7.9%), 358 (M, 11.4), 344 (12.3), 342 (60.7), 340 (93.9), 201 (100).

*2,5-Dichloro-1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one* **(4-7)**

A mixture of 3,3'-dichloro-2,2',4,6'-tetrahydroxy-4'-methoxy-6-methylbenzophenone **(4-14)** (0.15 g, 0.42 mmol) in water (20 ml) was refluxed for 18 h in an atmosphere of nitrogen. The cooled mixture was extracted with ethyl acetate. The organic extract was then washed with water and brine and dried ($MgSO_4$). After the solvent was removed the crude product was washed with acetone to give 2,5-dichloro-

1,6-dihydroxy-3-methoxy-8-methyl-9*H*-xanthen-9-one **(4-7)** (0.1 g, 70%) as yellow crystals, m.p. 276-278° (lit.[119] m.p. 296-297°) (Found: mol. wt. 339.9905. $C_{15}H_{10}O_5{}^{35}Cl_2$ requires: mol. wt. 339.9905). ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2.75, 3H, s, ArMe; 4.07, 3H, s, OMe; 6.76 and 6.90, each 1H, s, ArH; 13.85, 1H, s, OH. Mass spectrum *m/z* 344 (11.6%), 342 (72.7), 340 (M, 100.0). Standard t.l.c. R_F values: R_F (A) 0.56; R_F (B) 0.49; R_F (C) 0.45; R_F (E) 0.18; R_F (F) 0.61. Standard h.p.l.c. RI value: 0.83.

6.4.b. Synthesis of 2,5-Dichloro-6-*O*-methylnorlichexanthone

Ethyl 3-Chloro-2-hydroxy-4-methoxy-6-methylbenzoate **(4-15)**

An ethereal solution of diazomethane [from *p*-tolysulfonylmethylnitrosamide (26 g)][128] was added to a stirred solution of ethyl 3-chloro-2,4-dihydroxy-6-methylbenzoate[56] **(4-10)** (6 g, 29.6 mmol) in ether (150 ml) at 0° and the mixture stood for 2.5 h. Excess diazomethane was then destroyed by dropwise addition of acetic acid and the mixture was washed with water, brine and dried ($MgSO_4$). The ether was evaporated to give ethyl 3-chloro-2-hydroxy-4-methoxy-6-methylbenzoate **(4-15)** (7 g, 98%) which crystallized from ether as colourless crystals, m.p. 146° (lit.[39] m.p. 146-148°). ^{1}H n.m.r. ($CDCl_3$) δ 1.42, 3H, t, *J* 7Hz, CH_2CH_3; 2.55, 3H, s, ArMe; 3.92, 3H, s, OMe; 4.43, 2H, q, *J* 7Hz, CH_2CH_3; 6.33, 1H, s, ArH; 12.26, 1H, s, OH.

Ethyl 2-Benzyloxy-3-chloro-4-methoxy-6-methylbenzoate **(4-16)**

A mixture of ethyl 3-chloro-2-hydroxy-4-methoxy-6-methylbenzoate **(4-15)** (7 g, 29 mmol), benzyl bromide (4.1 ml, 35 mmol) and potassium carbonate (8 g, 58 mmol) in dry acetone (100 ml) was boiled under reflux for 24 h. The mixture was then

poured into a mixture of cold, dilute hydrochloric acid and extracted with ether. The ether extract was washed with water, brine and then dried ($MgSO_4$). After removal of the solvent the crude product was purified by column chromatography (SiO_2) using 3-7% ethyl acetate / light petroleum as eluant. The major band afforded *ethyl 2-benzyloxy-3-chloro-4-methoxy-6-methylbenzoate* (**4-16**) (4 g, 41%) as a yellow oil (Found: mol. wt. 334.0971. $C_{18}H_{19}O_4{}^{35}Cl$ requires: mol. wt. 334.0972). ^1H n.m.r. ($CDCl_3$) δ 1.27, t, *J* 7Hz, CH_2CH_3; 2.34, s, ArMe; 3.92, s, OMe; 4.29, q, *J* 7Hz, CH_2CH_3; 5.07, s, CH_2Ph; 6.59, s, ArH; 7.30-7.50, m, Ph. Mass spectrum *m/z* 336 (1.2%), 334 (M, 3.8), 2.89 (4.3), 200 (3.7), 198 (11.8), 91 (100.0).

2-Benzyloxy-3-chloro-4-methoxy-6-methylbenzoic Acid (**4-17**)

A mixture of ethyl 2-benzyloxy-3-chloro-4-methoxy-6-methylbenzoate (**4-16**) (3 g, 9 mmol), potassium hydroxide (2 g), water (9 ml), and dimethyl sulfoxide (50 ml) was stirred at 92-95° for 4.5 h in an atmosphere of nitrogen. The cooled mixture was poured into cold, dilute hydrochloric acid and extracted with ethyl acetate. The organic solution was washed with water, brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was crystallized from cyclohexane / ethyl acetate to give *2-benzyloxy-3-chloro-4-methoxy-6-methylbenzoic acid* (**4-17**) (2.5 g, 90%) as colourless needles, m.p. 175-176° (Found: C, 62.8; H, 4.7; Cl, 11.6. $C_{16}H_{15}O_4Cl$ requires: C, 62.7; H, 4.9; Cl, 11.6%). ^1H n.m.r. ($CDCl_3$) δ 2.51, s, ArMe; 3.95, s, OMe; 5.10, s, CH_2; 6.65, s, ArH; 7.35-7.50, m, Ph. Mass spectrum *m/z* 308 (0.7%), 306 (M, 2.1), 290 (0.4), 288 (1.0), 200 (3.8), 198 (12.0), 91 (100.0).

*2,5-Dichloro-1,3-dihydroxy-6-methoxy-8-methyl-9*H*-xanthen-9-one* **(4-8)**

Trifluoroacetic anhydride (1 ml) was added to a stirred solution of 2-benzyloxy-3-chloro-4-methoxy-6-methylbenzoic acid **(4-17)** (0.2 g, 0.65 mmol) and 1,3,5-tribenzyloxy-2-chlorobenzene **(3-21)** (0.54 g, 1.24 mmol) in 1,2-dichloroethane (20 ml). The mixture was boiled under reflux for 3 days. More trifluoroacetic anhydride (1 ml) was then added and the mixture refluxed for a further 2 days. The cooled solution was dissolved in ethyl acetate and washed with saturated aqueous potassium hydrogen carbonate solution, with water and finally with saturated brine. After drying ($MgSO_4$) the solvent was evaporated and the crude product was separated by radial chromatography (SiO_2) using 15-100% ethyl acetate / light petroleum as eluant to give *2,4,6-tribenzyloxy-3,3'-dichloro-4'-methoxy-6'-methylbenzophenone* **(4-19)** (0.1 g, 23%) (admixed with some tetrabenzyl derivative) as yellow gum.

Boron trichloride (5.3 mmol) in dry dichloromethane (5.3 ml) was then added to a solution of the above benzophenone (0.2 g, 0.28 mmol) in anhydrous dichloromethane (8 ml) at 0°. After this mixture was stirred at room tempertature for a further 1h, water was added and the mixture diluted with ethyl acetate. The organic layer was washed with water, brine and then dried ($MgSO_4$). After the removal of the solvent the crude product was separated by radial chromatography (SiO_2) using 20-50% ethyl acetate / light petroleum as eluant to give *2,5-dichloro-1,3-dihydroxy-6-methoxy-8-methyl-9*H*-xanthen-9-one* **(4-8)** (43 mg, 45%) as yellow crystals, m.p. 155-157° (Found: mol. wt. 339.9905. $C_{15}H_{10}O_5{}^{35}Cl_2$ requires: mol. wt. 339.9905). ^{1}H n.m.r. [$(CD_3)_2CO$] δ 2.90, 3H, s, ArMe; 4.05, 3H, s, OMe; 6.67, 1H, s, H4; 6.76, 1H, s, H7; 13.92, 1H, s, OH. Mass spectrum *m/z* 344 (11.0%), 342 (60.5), 340 (M, 100.0), 311 (3.5), 305 (1.6), 270 (2.0). Standard t.l.c. R_F values: R_F (A) 0.64; R_F (B) 0.51; R_F (C) 0.51; R_F (E) 0.32; R_F (F) 0.67. Standard h.p.l.c. RI value: 0.90.

6.4.c. 4,5-Dichloro-6-*O*-methylnorlichexanthone

3-Chloro-2-hydroxy-4-methoxy-6-methylbenzoic Acid **(4-18)**

A mixture of ethyl 3-chloro-2-hydroxy-4-methoxy-6-methylbenzoate **(4-15)** (2.1 g, 8.6 mmol), potassium hydroxide (2 g), water (9 ml), and dimethyl sulfoxide (50 ml) was stirred at 90-100° for 2 h in an atmosphere of nitrogen. The cooled mixture was poured into a mixture of ice and concentrated hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was crystallised from cyclohexane / ethyl acetate to give 3-chloro-2-hydroxy-4-methoxy-6-methylbenzoic acid **(4-18)** (1.1 g, 59%) as colourless prisms, which sublimated at 251-252°, m.p. 38-40° (lit.[39] m.p. 38°). ^1H n.m.r. [$(CD_3)_2CO$] δ 2.61, 3H, s, ArMe; 3.96, 3H, s, OMe; 6.62, 1H, s, ArH; 12.12, 1H, s, OH. Mass spectrum *m/z* 218 (4.3%), 216 (M, 13.2), 200 (34.6), 198 (100.0).

Benzyl 3-Chloro-4-(3'-chloro-2'-hydroxy-4'-methoxy-6'-methylbenzoyloxy)-2,6-dihydroxybenzoate **(4-21)**

A mixture of 3-chloro-2-hydroxy-4-methoxy-6-methylbenzoic acid **(4-18)** (0.25 g, 1.16 mmol) and benzyl 3-chloro-2,4,6-trihydroxybenzoate **(2-12)** (0.34 g, 1.16 mmol) was dried by azeotropic distillation with toluene. The mixture was then dissolved in toluene (6 ml), anhydrous tetrahydrofuran (2 ml) and trifluoroacetic anhydride (2.8 ml) and stirred at room temperature for 48 h. The mixture was diluted with ethyl acetate and washed with water, brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was purified by radial chromatography (SiO_2) using 2.5-20% ethyl acetate / light petroleum as eluant. The residue obtained from the major band was crystallized from ethyl acetate / cyclohexane to give *benzyl 3-chloro-4-*

(3'-chloro-2'-hydroxy-4'-methoxy-6'-methylbenzoyloxy)-2,6-dihydroxybenzoate (**4-21**) (0.12 g, 21%) as colourless needles, m.p. 158-159° (Found: C, 56.8; H, 4.2; Cl, 13.5. $C_{23}H_{18}O_8Cl_2$ requires: C, 56.0; H, 3.7; Cl, 14.4%). ^{1}H n.m.r. ($CDCl_3$) δ 2.70, 3H, s, ArMe; 3.97, 3H, s, OMe; 5.53, 2H, s, CH_2; 6.45, 2H, s, ArH; 7.43, 5H, s, Ph; 9.77, 10.47 and 11.49, each 1H, s, OH. Mass spectrum *m/z* 296 (0.1%), 294 (0.4), 216 (0.3), 200 (1.6), 198 (4.7), 186 (0.4), 91 (100.0).

2-(4'-Benzyloxycarbonyl-2'-chloro-3',5'-dihydroxyphenoxy)-3-chloro-4-methoxy-6-methylbenzoic Acid (**4-22**)

A solution of benzyl 3-chloro-4-(3'-chloro-2'-hydroxy-4'-methoxy-6'-methylbenzoyloxy)-2,6-dihydroxybenzoate (**4-21**) (0.23 g, 0.47 mmol) and anhydrous potassium carbonate (0.1 g, 0.7 mmol) in anhydrous dimethyl sulfoxide (4 ml) was stirred at room temperature for 2.5 h. The reaction mixture was then acidified with cold, dilute hydrochloric acid, extracted with ethyl acetate, and the ethyl acetate extract was washed with water, brine and then dried ($MgSO_4$). After evaporation of the solvent the crude product was purified by preparative t.l.c. (SiO_2) using 50% ethyl acetate as eluant. The major band afforded *2-(4'-benzyloxycarbonyl-2'-chloro-3',5'-dihydroxyphenoxy)-3-chloro-4-methoxy-6-methylbenzoic acid* (**4-22**) (0.16 g, 70%) as a colourless gum (Found: mol. wt. 492.0379. $C_{23}H_{18}O_8{}^{35}Cl_2$ requires: mol. wt. 492.0379). ^{1}H n.m.r. [$(CD_3)_2CO$] δ 2.47, 3H, s, Me; 4.00, 3H, s, OMe; 5.62, 2H, s, CH_2; 5.66 and 7.11, each 1H, s, ArH; 7.41-7.57, 5H, m, Ph; 9.89 and 10.85, each 1H, s, OH. Mass spectrum *m/z* 494 (0.3%), 492 (M, 0.4), 450 (0.3), 448 (0.4), 430 (0.5), 340 (1.4), 200 (2.0), 198 (11.6), 91 (100.0).

*Benzyl 4,5-dichloro-1,3-dihydroxy-6-methoxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylate* **(4-23)**

The foregoing carboxylic acid **(4-22)** (40 mg, 0.08 mmol) was dried by azeotropic distillation with toluene and then dissolved in a mixture of anhydrous toluene (2.5 ml) and trifluoroacetic anhydride (1 ml). The mixture was stirred at room temperature for 22 h and then the solvent was removed and the residue washed with ethyl acetate to give *benzyl 4,5-dichloro-1,3-dihydroxy-6-methoxy-8-methyl-9-oxo-9*H*-xanthen-2-carboxylate* **(4-23)** (35 mg, 92%) as a pale yellow microcrystalline solid, m.p. 252-253° (Found: mol. wt. 474.0275. $C_{23}H_{16}O_7{}^{35}Cl_2$ requires: mol. wt. 474.0273). ^{1}H n.m.r. [$(CD_3)_2CO$] δ 2.83, 3H, s, ArMe; 4.04, 3H, s, OMe; 5.36, 2H, s, CH_2; 7.18, 1H, s, H7; 7.40-7.48, 5H, m, Ph. Mass spectrum *m/z* 476 (0.5%), 474 (M, 0.9), 370 (1.2), 368 (6.6), 366 (10.2), 108 (27.9), 91 (100.0).

*4,5-Dichloro-1,3-dihydroxy-6-methoxy-8-methyl-9*H*-xanthen-9-one* **(4-9)**

Boron trichloride (0.8 mmol) in dichloromethane (0.8 ml) was added to a solution of the benzyl ester (35 mg, 0.074 mmol) in dry dichloromethane (5 ml) at 0° and the mixture stirred at room temperature for 4 h. Water (5 ml) was then added to the reaction mixture followed by excess ethyl acetate. The organic layer was washed with water, brine and then dried ($MgSO_4$). Removal of the solvent yielded the crude 4,5-dichloro-1,3-dihydroxy-6-methoxy-8-methyl-9*H*-xanthen-9-one-2-carboxylic acid **(4-24)** as yellow crystals. A solution of this acid in dimethyl sulfoxide (10 ml), potassium hydroxide (0.1 g) and water (3 ml) was stirred and heated under a nitrogen atmosphere at 130° for 2 h. The cooled mixture was poured into cold, dilute hydrochloric acid, extracted with ethyl acetate and the organic extract was washed with water, saturated brine and then dried ($MgSO_4$). After removal of the solvent the residue was purified by preparative t.l.c. (SiO_2) using 33% ethyl actate / hexane as eluant to give *4,5-dichloro-*

*1,3-dihydroxy-6-methoxy-8-methyl-9*H*-xanthen-9-one* **(4-9)** (20 mg, 69%) as yellow crystals, m.p. 180-182° (Found: mol. wt. 339.9905. $C_{15}H_{10}O_5{}^{35}Cl_2$ requires: mol. wt. 339.9905). ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2.81, 3H, s, ArMe; 4.03, 3H, s, OMe; 6.29, 1H, s, H2; 7.14, 1H, s, H7; 13.08, 1H, s, OH. Mass spectrum *m/z* 344 (2.0%), 342 (11.4), 340 (M, 17.9), 309 (2.7), 299 (2.1), 297 (3.0), 184 (100.0). Standard t.l.c. R_F values: R_F (A) 0.60; R_F (B) 0.51; R_F (C) 0.48; R_F (E) 0.30; R_F (F) 0.65. Standard h.p.l.c. RI value: 1.03. The t.l.c. and h.p.l.c. behaviour of synthetic **(4-9)** was identical with that of one of the minor metabolites from an Australian *Dimelaena* lichen.

*4,5-Dichloro-1,3, 6-trimethoxy-8-methyl-9*H*-xanthen-9-one*

A mixture of 4,5-dichloro-1,3-dihydroxy-6-methoxy-8-methyl-9*H*-xanthen-9-one **(4-9)** (10 g, 0.03 mmol), dimethyl sulfate (0.01 ml, 0.1 mmol) and potassium carbonate (14 mg, 0.1 mmol) in dry acetone (20 ml) was refluxed for 17 h. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water and brine and then dried ($MgSO_4$). The crude product after the removal of the solvent was separated by preparative t.l.c. (SiO_2) using 25% ethyl acetate / hexane to yield *4,5-dichloro-1,3, 6-trimethoxy-8-methyl-9*H*-xanthen-9-one* (8 mg, 72%) as yellow crystals, m.p. 112-114° (Found: mol. wt. 368.0219. $C_{17}H_{14}O_5{}^{35}Cl_2$ requires: mol. wt. 368.0218). ^{1}H n.m.r. [$(CD_3)_3CO$] δ 2.77, 3H, s, ArMe; 3.99, 4.04 and 4.09, each 3H, s, OMe; 6.78 1H, s, H2; 7.01, 1H, s, H7. Mass spectrum *m/z* 372 (5.3%), 370 (29.5), 368 (45.5), 354 (14.0), 352 (58.1), 350 (100.0).

6.5. Synthesis of Thiomelin Derivatives

6.5.a. Synthesis of 2,4-Dichloro-1-hydroxy-7-methoxy-6,8-dimethyl-9*H*-xanthen-9-one (TH2)

Methyl 2,6-Dihydroxybenzoate **(5-6)**

An ethereal solution of diazomethane [prepared[128] from *p*-toluenesulfonylmethylnitrosamide (43 g)] was slowly added to a solution of 2,6-dihydroxybenzoic acid **(5-5)** (20 g, 0.13 mol) in ethanol (100 ml). After this addition, the excess diazomethane was destroyed by addition of glacial acetic acid (several drops) and then the mixture was washed with sodium hydrogen carbonate, brine and dried ($MgSO_4$). The ether solution was evaporated to give the product **(5-6)** (11.6 g, 53%) which was crystallized from cyclohexane as yellow crystals, m.p. 53-55° (lit.[97] m.p. 54-58°). ^1H n.m.r. ($CDCl_3$) δ 4.08, 3H, s, CO_2Me; 6.48, 2H, d, *J* 9Hz, H3 and H5; 7.27, 1H, t, *J* 9Hz, H4; 9.62, 2H, s, OH.

Methyl 3,5-Dichloro-2,6-dihydroxybenzoate **(5-7)**

A solution of sulfuryl chloride (15 ml, 0.21 mol) in anhydrous ether (40 ml) was added dropwise to a stirred solution of methyl 2,6-dihydroxybenzoate **(5-6)** (11.6 g, 0.07 mol) in anhydrous ether (200 ml) over a period of 15 min and the mixture stirred at room temperature for 2 h. The precipitated product was filtered and recrystallized from cold ether to give methyl 3,5-dichloro-2,6-dihydroxybenzoate **(5-7)** (10 g, 61%) as colourless crystals, m.p. 162-165° (lit.[34] m.p. 163-164°). ^1H n.m.r. ($CDCl_3$) δ 4.05, 3H, s, CO_2Me; 7.50, 1H, s, ArH; 10.01, 2H, s, OH.

Methyl 3,5-Dichloro-2,6-dimethoxybenzoate **(5-8)**

A solution of dimethyl sulfate (10 ml, 0.105 mol) in anhydrous acetone (20 ml) was added dropwise to a stirred solution of methyl 3,5-dichloro-2,6-dihydroxybenzoate **(5-7)** (10 g, 0.042 mol) and potassium carbonate (30 g) in anhydrous acetone (300 ml) and stirring continued at room temperature for 22 h. The mixture was then filtered, and the filtrate evaporated. The residue was dissolved in ether, and the ethereal solution was washed with sodium hydroxide solution (5%), concentrated ammonium chloride solution, water, brine and then dried ($MgSO_4$). The ether was then evaporated to yield methyl 3,5-dichloro-2,6-dimethoxybenzoate **(5-8)**[34] (10.7 g, 96%) as an yellow oil. ^1H n.m.r. ($CDCl_3$) δ 3.88, 6H, s, OMe; 3.95, 3H, s, CO_2Me; 7.45, 1H, s, ArH.

3,5-Dichloro-2,6-dimethoxybenzoic Acid **(5-9)**

A mixture of methyl 3,5-dichloro-2,6-dimethoxybenzoate **(5-8)** (10.7 g, 40 mmol), potassium hydroxide (11.9 g), water (21 ml), and dimethyl sulfoxide (370 ml) was stirred at 85° for 20 h in an atmosphere of nitrogen. The cooled reaction mixture was poured into a mixture of ice and concentrated hydrochloric acid and extracted with ether. The ethereal solution was washed with water, brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was crystallized from light petroleum to give 3,5-dichloro-2,6-dimethoxybenzoic acid **(5-9)** (8.2 g, 81%) as colourless crystals, m.p. 95-97° (lit.[34] m.p. 99-100°). ^1H n.m.r. ($CDCl_3$) δ 3.92, 6H, s, OMe; 7.46, 1H, s, ArH; 9.79, 1H, bs, OH. Mass spectrum *m/z* 254 (7.5%), 252 (46.0), 250 (M, 71.8), 235 (10.3), 233 (15.3), 218 (19.2), 205 (40.6), 175 (100.0).

4-Hydroxy-3,5-dimethylbenzaldehyde **(5-11)**

A mixture of 2,6-dimethylphenol (2,6-xylenol) **(5-10)** (4.9 g, 0.04 mol), hexamethylenetetramine (10.2 g, 0.073 mol) and 50% acetic acid (35 ml) was stirred and heated to 105-110° for 4 h in nitrogen atmosphere. Concentrated hydrochloric acid (15.3 ml) was then added and the mixture was heated under reflux for a further 10 min. The cooled reaction mixture was diluted with water (300 ml) and extracted with ether. The ethereal layer was washed with water, dilute sodium hydrogen carbonate, brine and then dried ($MgSO_4$). After the removal of ether the residue was crystallized from cyclohexane to give 4-hydroxy-3,5-dimethylbenzaldehyde **(5-11)** (4.5 g, 75%) as pale yellow crystals, m.p. 111-113° (lit.[124] m.p. 115-116°). ^1H n.m.r. ($CDCl_3$) δ 2.30, 6H, s, Me; 7.53, 2H, s, ArH; 9.79, 1H, s, CHO. Mass spectrum *m/z* 150 (M, 71.1%), 149 (100.0), 121 (24.2).

4-Methoxy-3,5-dimethylbenzaldehyde **(5-12)**

A mixture of the foregoing aldehyde **(5-11)** (4.5 g, 0.03 mol), dimethyl sulfate (3.4 ml, 0.036 mol) and anhydrous potassium carbonate (12 g, 0.09 mol) in dimethylformamide (30 ml) was stirred at room temperature for 16 h. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and extracted with ether. The ether extract was washed with water and brine and dried ($MgSO_4$). Removal of the solvent yielded the product **(5-12)** (4.6 g, 93%) as yellow oil, b.p. 245° (lit.[55] b.p. 257°). ^1H n.m.r. ($CDCl_3$) δ 2.34, 6H, s, ArMe; 3.77, 3H, s, OMe; 7.55, 2H, s, ArH; 9.88, 1H, s, CHO. Mass spectrum *m/z* 165 (10.2%), 164 (M, 100.0), 163 (99.3), 149 (16.0), 121 (11.6).

4-Methoxy-3,5-dimethylphenol **(5-14)**

A solution of 4-methoxy-3,5-dimethylbenzaldehyde **(5-12)** (4.5 g, 0.027 mol) in anhydrous dichloromethane (40 ml) was added with stirring over 40 min to a solution of 50-60% *m*-chloroperbenzoic acid (0.063 mol) in anhydrous dichloromethane (200 ml) at room temperature. The solution was stirred for 16 h and then the solvent was removed under reduced pressure. The residue was redissolved in ethyl acetate and the solution was washed with a solution of 10% sodium hydrogen carbonate until effervesence ceased, then with saturated brine. The residue left on removal of the solvent was a mixture of the formate and the required phenol.

This mixture was then dissolved in methanol (100 ml) and aqueous potassium hydroxide (10%, 100 ml) was added at 0° in a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 1 h, poured into cold, dilute hydrochloric acid and then extracted with ether. The ether extracted was washed with potassium carbonate solution, water, brine and then dried ($MgSO_4$). After the removal of solvent the residue was crystallized from cyclohexane to give 4-methoxy-3,5-dimethylphenol **(5-14)** (2.3 g, 56%) as pale yellow needles, m.p. 84-86° (lit.[14] m.p. 84-85°). ^1H n.m.r. ($CDCl_3$) δ 2.22, 6H, s, ArMe; 3.66, 3H, s, OMe; 6.46, 2H, s, ArH.

1,4-Dimethoxy-2,6-dimethylbenzene **(5-15)**

A mixture of 4-methoxy-3,5-dimethylphenol **(5-14)** (2.3 g, 15 mmol), dimethyl sulfate (1.7 ml, 18 mmol) and potassium carbonate (6.2 g, 45 mmol) in anhydrous acetone (50 ml) was stirred at room temperature for 20 h. The reaction mixture was poured into a mixture of ice and hydrochloric acid and extracted with ether. The organic extract was washed with water, brine and dried ($MgSO_4$). After removal of solvent the residue was purified by flash chromatography (SiO_2) using 8.5% ethyl acetate / light

petroleum as eluant to give *1,4-dimethoxy-2,6-dimethylbenzene* **(5-15)** (1.9 g, 75%) as colourless oil (Found: mol. wt. 166.0993. $C_{10}H_{14}O_2$ requires: mol. wt. 166.0994). ^1H n.m.r. ($CDCl_3$) δ 2.25, 6H, s, ArMe; 3.66, 3.72, each 3H, s, OMe; 6.53, 2H, s, ArH. Mass spectrum *m/z* 166 (M, 56.8%), 152 (10.6), 151 (100.0).

3,5-Dichloro-2,3',6,6'-tetramethoxy-2',4'-dimethylbenzophenone **(5-16)**

Trifluoroacetic anhydride (5.7 ml) was added to a stirred solution of 1,4-dimethoxy-2,6-dimethylbenzene **(5-15)** (0.66 g, 4 mmol) and 3,5-dichloro-2,6-dimethoxybenzoic acid **(5-9)** (1 g, 4 mmol) in 1,2-dichloroethane (10 ml) at 0°. The mixture was then refluxed for 18 h. The cooled solution was dissolved in ethyl acetate and washed with 1M sodium hydroxide solution, with water and finally with saturated brine. After drying ($MgSO_4$) the solvent was evaporated to give the crude product which was crystallized from cyclohexane to afford *3,5-dichloro-2,3',6,6'-tetramethoxy-2',4'-dimethylbenzophenone* **(5-16)** (0.8 g, 50%) as colourless prisms, m.p. 136-137° (Found: mol. wt. 398.0687. $C_{19}H_{20}O_5{}^{35}Cl_2$ requires: mol. wt. 398.0688). ^1H n.m.r. ($CDCl_3$) δ 2.30, 2.37, each 3H, s, ArMe; 3.51, 3H, s, OMe; 3.63, 6H, s, OMe; 3.69, 3H, s, OMe; 6.54, 1H, s, H5'; 7.40, 1H, s, H4. Mass spectrum *m/z* 402 (2.6%), 400 (14.1), 398 (M, 20.5), 371 (11.8), 369 (69.8), 367 (100.0).

3,5-Dichloro-2,3',6'-trihydroxy-6-methoxy-2',4'-dimethylbenzophenone **(5-18)** *and 3,5-Dichloro-2,3',6,6'-tetrahydroxy-2',4'-dimethylbenzophenone* **(5-17)**

Boron tribromide (0.2 ml, 2.08 mmol) was added to a solution of 3,5-dichloro-2,3',6,6'-tetramethoxy-2',4'-dimethylbenzophenone **(5-16)** (20 mg, 0.05 mmol) in dichloromethane (3 ml) at -10°. The mixture was stirred at this temperature for 2 h and at room temperature for 20 min. The mixture was then diluted with water and the

solvent was evaporated. The residue obtained was extracted into ethyl acetate and the extract was washed with water, brine and then dried ($MgSO_4$). The residue left after removal of the solvent was purified by radial chromatography (SiO_2) using 20-50% ethyl acetate / light petroleum as eluant. The faster band yielded *3,5-dichloro-2,3',6'-trihydroxy-6-methoxy-2',4'-dimethylbenzophenone* **(5-18)** (6 mg, 34%) which crystallized from the eluant as pale yellow crystals, m.p. 160-161° (Found: mol. wt. 356.0218. $C_{16}H_{14}O_5{}^{35}Cl_2$ requires: mol. wt. 356.0219). ^1H n.m.r. ($CDCl_3$) δ 1.95, 2.26, each 3H, s, ArMe; 3.47, 3H, s, OMe; 6.65, 1H, s, H5'; 7.54, 1H, s, H4; 9.87, 2H, s, OH. Mass spectrum *m/z* 358 (11.1%), 356 (M, 17.6), 327 (36.8), 326 (20.4), 325 (59.0), 164 (100.0).

The slower band afforded *3,5-dichloro-2,3',6,6'-tetrahydroxy-2',4'-dimethylbenzophenone* **(5-17)** (10 mg, 58%) which crystallized from the eluant as pale yellow crystals, m.p. 165-167° (Found: mol. wt. 342.0059. $C_{15}H_{12}O_5{}^{35}Cl_2$ requires: mol. wt. 342.0062). ^1H n.m.r. ($CDCl_3$) δ 2.05, 2.26, each 3H, s, ArMe; 6.63, 1H, s, H5'; 7.53, 1H, s, H4; 9.00, 2H, s, OH. Mass spectrum *m/z* 346 (1.7%), 344 (10.6), 342 (M, 25.7), 340 (14.0), 327 (15.7), 325 (16.5), 324 (10.5), 138 (100.0).

*2,4-Dichloro-1,7-dihydroxy-6,8-dimethyl-9*H*-xanthen-9-one* **(5-19)**

A mixture of 3,5-dichloro-2,3',6-trihydroxy-6'-methoxy-2',4'-dimethylbenzophenone **(5-18)** (20 mg, 0.062 mmol) and water (10 ml) was heated up to 120° for 16 h in a sealed tube. The mixture was then cooled and extracted with ethyl acetate. The organic layer was washed with water, brine and dried ($MgSO_4$). The residue obtained on removal of the solvent was purified by radial chromatography (SiO_2) using 20% ethyl acetate / light petroleum as eluant. The major band yielded *2,4-dichloro-1,7-dihydroxy-6,8-dimethyl-9*H*-xanthen-9-one* **(5-19)** (18 mg, 90%) which crystallized from the eluant as pale yellow crystals, m.p. 188-190° (Found: mol. wt.

323.9956. $C_{15}H_{10}O_4{}^{35}Cl_2$ requires: mol. wt. 323.9956). ^1H n.m.r. ($CDCl_3$) δ 2.43, 2.83, each 3H, s, ArMe; 7.28, 1H, s, H5; 7.70, 1H, s, H3; 13.71, 1H, s, OH. Mass spectrum *m/z* 328 (11.4%), 326 (66.2), 324 (M, 100.0), 295 (31.1). Standard t.l.c. R_F values: R_F (A) 0.62; R_F (B) 0.70; R_F (C) 0.65; R_F (E) 0.46; R_F (F) 0.83. Standard h.p.l.c. RI value: 1.58. The synthetic sample was found to be identical (t.l.c., h.p.l.c.) with a minor metabolite of the lichen *Rinodina thiomela.*

*2,4-Dichloro-1-hydroxy-7-methoxy-6,8-dimethyl-9*H*-xanthen-9-one (TH2)* **(1-38)**

A mixture of 2,4-dichloro-1,7-dihydroxy-6,8-dimethyl-9*H*-xanthen-9-one (**5-19**) (10 mg, 0.03 mmol), dimethyl sulfate (9.3 mg, 0.074 mmol) and potassium carbonate (0.05 g, 0.36 mmol) in anhydrous acetone (20 ml) was refluxed for 3 h. The mixture was poured into ice-hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, brine and dried ($MgSO_4$). After removal of the solvent the crude product above (10 mg) was azeotroped with toluene, then dissolved in anhydrous dichloromethane (10 ml) and treated with a solution of boron trichloride (0.3 mmol) in dichloromethane (0.3 ml) at 0°. The mixture was stirred at room temperature for 24 h, then diluted with water and extracted with ethyl acetate. The organic extract was washed with water, brine and dried ($MgSO_4$). The residue after removal of solvent was purified by preparative t.l.c. (SiO_2) using 23% ethyl acetate / light petroleum as eluant. The major band afforded *2,4-dichloro-1-hydroxy-7-methoxy-6,8-dimethyl-9*H*-xanthen-9-one (TH2)* **(1-38)** (8 mg, 78%) which crystallized from the eluant as pale yellow crystals, m.p. 157-158° (Found: mol. wt. 338.0110. $C_{16}H_{12}O_4{}^{35}Cl_2$ requires: mol. wt. 338.0113). ^1H n.m.r. ($CDCl_3$) δ 2.45, 2.83, each 3H, s, ArMe; 3.74, 3H, s, OMe; 7.28, 7.70, each 1H, s, ArH; 13.67, 1H, s, OH. Mass spectrum *m/z* 342 (5.3%), 340 (28.8), 338 (M, 48.2), 325 (65.1), 323 (100.0). Standard t.l.c. R_F values: R_F (A) 0.79; R_F (B) 0.88; R_F (C) 0.86; R_F (E) 0.72; R_F (F) 0.90. Standard h.p.l.c. RI

value: 2.92. This synthetic sample was found to be identical (t.l.c., h.p.l.c., ^{1}H n.m.r., m.s.) with the natural material isolated from *Rinodina thiomela*.[41]

6.5.b. Synthesis of 2,4-Dichloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthen-9-one (TH3)

*2,4-Dichloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthen-9-one (TH3)* **(5-4)**

Boron tribromide (0.07 ml, 0.73 mmol) was added to a stirred solution of 2,4-dichloro-1,8-dihydroxy-5-methoxy-6-methyl-9*H*-xanthen-9-one (thiomelin) **(1-36)** (8 mg, 0.024 mmol) in anhydrous dichloromethane (5 ml) at 0° and the mixture was stirred at room tempertature for 1.2 h. Water was added and the mixture was diluted with ethyl acetate. The organic extract was washed with water, brine and then dried ($MgSO_4$). After the removal of the solvent the crude product was purified on preparative t.l.c. (SiO_2) using 25% ethyl acetate / light petroleum as eluant. The major band afforded *2,4-dichloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthen-9-one (TH3)* **(5-4)** (6 mg, 76%) which crystallized from the eluant as yellow crystals, m.p. 212-213° (Found: mol. wt. 325.9748. $C_{14}H_8O_5{}^{35}Cl_2$ requires: mol. wt. 325.9749). ^{1}H n.m.r. [$(CD_3)_2CO$] δ 2.59, 3H, s, Me; 6.74 and 7.99, each 1H, s, ArH; 8.18 and 10.82, each 1H, s, OH; 12.60, 1H, b, OH. Mass spectrum *m/z* 330 (1.8%), 328 (9.6), 326 (M, 16.6), 205 (1.3), 204 (1.1), 181 (1.0), 42.7 (100.0). Standard t.l.c. R_F values: R_F (A) 0.69; R_F (B) 0.70; R_F (C) 0.72; R_F (E) 0.47; R_F (F) 0.85. Standard h.p.l.c. RI value: 0.27. This synthetic sample was found to be identical (t.l.c., h.p.l.c.) with a minor metabolite of the lichen *Rinodina thiomela*.

6.5.c. Synthesis of 2-Dechlorothiomelin and Derivatives

i. Using an Organolithium Intermediate

3-Chloro-2,6-dihydroxybenzoic Acid **(5-22)**

A solution of sulfuryl chloride (5.2 ml, 64 mmol) in anhydrous ether (60 ml) was added dropwise to a stirred solution of 2,6-dihydroxybenzoic acid **(5-5)** (9 g, 58 mmol) in anhydrous ether (300 ml) over a period of 15 min. The mixture was then stirred at room temperature for 26 h. The solvent was removed and the residue crystallized from water to give 3-chloro-2,6-dihydroxybenzoic acid **(5-22)** (7.6 g, 69 %) as pale pink crystals, m.p. 190-193° (lit.[25] m.p. 189°) (Found: C, 44.9; H, 2.4; Cl, 19.1. $C_7H_5O_4Cl$ requires: C, 44.6; H, 2.7; Cl, 18.8%). ^1H n.m.r. [$(CD_3)_2CO$] δ 6.47, 1H, d, *J* 8.8Hz, H5; 7.41, 1H, d, *J* 8.8Hz, H4.

Methyl 3-Chloro-2,6-dimethoxybenzoate **(5-23)**

A mixture of 3-chloro-2,6-dihydroxybenzoic acid **(5-22)** (7.6 g, 40 mmol), dimethyl sulfate (25 ml, 233 mmol) and potassium carbonate (22.1 g, 160 mmol) in anhydrous acetone (180 ml) was refluxed for 22 h. The cooled mixture was poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ether. The ethereal solution was washed with saturated sodium carbonate solution, water, brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was crystallized from cyclohexane to give methyl 3-chloro-2,6-dimethoxybenzoate **(5-23)** (6 g, 65%) as colourless prisms, m.p. 89° (lit.[25] m.p. 84°). ^1H n.m.r. ($CDCl_3$) δ 3.81, 3.89, 3.92, each 3H, s, OMe; 6.64, 1H, d, *J* 8.8Hz, H5; 7.34, 1H, d, *J* 8.8Hz, H4. Mass spectrum *m/z* 232 (14.6%), 230 (M, 45.2), 201 (32.5), 199 (100.0).

3-Chloro-2,6-dimethoxybenzoic Acid **(5-24)**

A solution of methyl 3-chloro-2,6-dimethoxybenzoate **(5-23)** (2.24 g, 9.7 mmol) and potassium hydroxide (1.1 g) in 50% aqueous methanol (10 ml) was refluxed for 2 h in an atmosphere of nitrogen. The cooled mixture was poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ethyl acetate. The organic layer was washed with water, brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was crystallized from cyclohexane / ethyl acetate to give 3-chloro-2,6-dimethoxybenzoic acid **(5-24)** (2.1 g, 96%) as colourless plates, m.p. 135-136° (lit.[25] m.p. 133°). ^1H n.m.r. ($CDCl_3$) δ 3.83 and 3.86, each 3H, s, OMe; 6.87, 1H, d, *J* 9.6 Hz, H5; 7.42, 1H, d, *J* 9.6 Hz, H4. Mass spectrum *m/z* 218 (28.8%), 216 (M, 86.2), 199 (30.9), 141 (100.0).

2,4-Dihydroxy-6-methylbenzaldehyde **(5-27)**

Freshly distilled phosphoryl chloride (21.3 ml, 0.23 mol) was added dropwise to a solution of orcinol **(5-26)** (26.4 g, 0.213 mol) in anhydrous *N,N*-dimethylformamide (40 ml, 0.52 mol) at 0° over 30 min. After 2.5 h at room temperature, the orange viscous mass was diluted with water (500 ml). The mixture was saturated with sodium acetate and stood overnight. The mixture was then diluted with water (300 ml) and extracted with ethyl acetate. The organic extract was washed with water, brine and dried ($MgSO_4$). Removal of the solvent gave 2,4-dihydroxy-6-methylbenzaldehyde **(5-27)** (22.6 g, 70%) which crystallized from cyclohexane in pale brown crystals, m.p. 180-183° (lit.[55] m.p. 181-182°). ^1H n.m.r. ($CDCl_3$) δ 2.52, 3H, s, Me; 6.21, 2H, s, ArH; 10.09, 1H, s, CHO; 12.35 and 13.04, each 1H, s, OH.

2,4-Dimethoxy-6-methylbenzaldehyde **(5-28)**

A mixture of 2,4-hydroxy-6-methylbenzaldehyde **(5-27)** (6 g, 39.5 mmol), dimethyl sulfate (8.2 ml, 86.9 mmol), potassium carbonate (21.8 g, 160 mmol) and anhydrous acetone (100 ml) was refluxed for 18 h. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and extracted with ether. The ether extract was washed with water, brine and then dried ($MgSO_4$). Removal of the solvent yielded the crude product which was purified by column chromatography (SiO_2) using 5-20% ethyl acetate / light petroleum as eluant. The major band afforded 2,4-dimethoxy-6-methylbenzaldehyde **(5-28)** (7 g, 98%) which crystallized from the eluant as colourless needles, m.p. 64-65° (lit.[75] m.p. 62-63°). ^1H n.m.r. ($CDCl_3$) δ 2.57, 3H, s, ArMe; 3.84 and 3.86, each 3H, s, OMe; 6.31, 2H, s, ArH; 10.47, 1H, s, CHO.

2-Hydroxy-4-methoxy-6-methylbenzaldehyde **(5-29)**

A solution of boron trichloride (0.156 mol) in dichloromethane (156 ml) was added dropwise to a stirred solution of 2,4-dimethoxy-6-methylbenzaldehyde **(5-28)** (7 g, 0.039 mol) in anhydrous dichloromethane (100 ml) at -10° over a period of 45 min. The mixture was stirred at 0° for 1 h and at room temperature for 2.5 h. The solvent was then removed and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with water and brine and dried ($MgSO_4$). After the removal of the solvent the crude product was purified by flash chromatography (SiO_2) using 17% ethyl acetate / light petroleum as eluant. The major band afforded 2-hydroxy-4-methoxy-6-methylbenzaldehyde **(5-29)** (6 g, 93%) which crystallized from the eluant as yellow needles, m.p. 63-66° (lit.[75] m.p. 65°). ^1H n.m.r. ($CDCl_3$) δ 2.45, 3H, s, ArMe; 3.79, 3H, s, OMe; 6.24, 2H, s, ArH; 10.18, 1H, s, CHO; 12.60, 1H, s, OH.

2-Benzyloxy-4-methoxy-6-methylbenzaldehyde **(5-30)**

A mixture of 2-hydroxy-4-methoxy-6-methylbenzaldehyde **(5-29)** (6 g, 36 mmol), benzyl bromide (6.42 ml, 54 mmol) and potassium carbonate (17 g, 123 mmol) in anhydrous dimethylformamide (70 ml) was stirred and heated at 60° for 18 h. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ether. The ether extract was washed with water, brine and then dried ($MgSO_4$). After removal of the solvent the crude product was crystallized from cyclohexane to give *2-benzyloxy-4-methoxy-6-methylbenzaldehyde* **(5-30)** (7.6 g, 82%) as colourless crystals, m.p. 75° (Found: C, 75.2; H, 6.3. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3%). ^1H n.m.r. ($CDCl_3$) δ 2.59, 3H, s, ArMe; 3.83, 3H, s, OMe; 5.13, 2H, s, CH_2Ph; 6.32 and 6.35, each 1H, s, ArH; 7.39, 5H, m, Ph; 10.52, 1H, s, CHO. Mass spectrum *m/z* 256 (M, 3.0%), 227 (1.1), 91 (100.0).

2-Benzyloxy-4-methoxy-6-methylphenol **(5-32)**

A solution of 2-benzyloxy-4-methoxy-6-methylbenzaldehyde **(5-30)** (6.8 g, 26.6 mmol) in anhydrous dichloromethane (40 ml) was added with stirring over 40 min to a solution of 50-60% *m*-chloroperbenzoic acid (63 mmol) in anhydrous dichloromethane (250 ml) at room temperature. The solution was stirred for 20 h and then the solvent was removed under reduced pressure. The residue was redissolved in ethyl acetate and this solution was washed with 10% sodium hydrogen carbonate until effervescence ceased, then with saturated brine. The residue left on removal of the solvent was found to be a mixture of the formate **(5-31)** and the corresponding phenol **(5-32)**.

The crude formate mixture obtained above was then dissolved in methanol (100 ml) and aqueous potassium hydroxide (10%, 100 ml) was added at 0° in a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 2 h, then poured

into cold, dilute hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with potassium carbonate, water, brine and then dried ($MgSO_4$). After the removal of solvent the residue was purified by flash chromatography (SiO_2) using 7.5% ethyl acetate / light petroleum as eluant. The major band afforded *2-benzyloxy-4-methoxy-6-methylphenol* (**5-32**) (3.2 g, 49%) which crystallized from the eluant as colourless needles, m.p. 67-68° (Found: C, 73.6; H, 6.7. $C_{15}H_{16}O_3$ requires: C, 73.8; H, 6.6%). ^1H n.m.r. ($CDCl_3$) δ 2.24, 3H, s, ArMe; 3.72, 3H, s, OMe; 5.06, 2H, s, CH_2Ph; 6.30 and 6.41, each 1H, d, *J* 3.2Hz, ArH; 7.38, 5H, m, Ph. Mass spectrum *m/z* 244 (M, 5.1%), 153 (75.7), 125 (14.7), 91 (100.0).

3-Benzyloxy-2,5-dimethoxytoluene (**5-33**)

A mixture of 2-benzyloxy-4-methoxy-6-methylphenol (**5-32**) (3.1 g, 12.7 mmol), dimethyl sulfate (1.6 ml, 16.5 mmol), potassium carbonate (5.3 g, 38 mmol) and anhydrous acetone (50 ml) was refluxed for 18 h. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ether. The ether extract was washed with water, brine and then dried ($MgSO_4$). Removal of the solvent yielded the crude product which was purified by flash chromatography (SiO_2) using 7.5-25% ethyl acetate / light petroleum as eluant. The major band yielded *3-benzyloxy-2,5-dimethoxytoluene* (**5-33**) (2 g, 61%) which crystallized from the eluant as pale yellow needles, m.p. 36-40° (Found: C, 74.2; H, 7.2. $C_{16}H_{18}O_3$ requires: C, 74.4; H, 7.0%). ^1H n.m.r. ($CDCl_3$) δ 2.25, 3H, s, ArMe; 3.71 and 3.78, each 3H, s, OMe; 5.07, 2H, s, $PhCH_2$; 6.29, 1H, d, *J* 3.2Hz, H4; 6.39, 1H, d, *J* 3.2Hz, H6; 7.32-7.45, 5H, m, Ph. Mass spectrum *m/z* 258 (M, 9.6%), 167 (12.3), 139 (24.1), 91 (100.0).

2'-Benzyloxy-3-chloro-2,3',6,6'-tetramethoxy-4'-methylbenzophenone **(5-35)**

(a) n-Butyllithium (5.52 mmol, 3.45 ml of 1.6 M solution in hexane) was added slowly to a solution of 3-benzyloxy-2,5-dimethoxytoluene **(5-33)** (1.38 g, 5.3 mmol) in anhydrous hexane (30 ml) at -78° under an atmosphere of dry nitrogen. The resultant solution was stirred at room temperature for 4 h.

(b) A solution of 3-chloro-2,6-dimethoxybenzoic acid **(5-24)** (1.18 g, 5.48 mmol) and thionyl chloride (6 ml) in anhydrous toluene (30 ml) was refluxed for 4 h. The toluene was then distilled under reduced pressure and the crude acid chloride was azeotroped three times with toluene to remove any residual thionyl chloride. The residue was then redissolved in anhydrous toluene (30 ml).

(c) The lithiation mixture (a) was added dropwise to the acid chloride solution (b) at -78° over a period of 20 min in an atmosphere of dry nitrogen. The solution was then stirred at room temperature for 1.5 h, poured into a mixture of ice and concentrated hydrochloric acid and extracted with ether. The ether extract was washed with water, brine and then dried ($MgSO_4$). The crude product obtained on removal of the solvent was purified by column chromatography (SiO_2) using 15-40% ethyl acetate / light petroleum as eluant. The major band afforded *2'-benzyloxy-3-chloro-2,3',6,6'-tetramethoxy-4'-methylbenzophenone* **(5-35)** (0.6 g, 25%) as a yellow oil (Found: mol. wt. 456.1340. $C_{25}H_{25}O_6{}^{35}Cl$ requires: mol. wt. 456.1340). ^1H n.m.r. ($CDCl_3$) δ 2.28, 3H, s, ArMe; 3.56, 3.65, 3.67 and 3.72, each 3H, s, OMe; 4.88, 2H, s, CH_2Ph; 6.49, 1H, s, H5'; 6.52, 1H, d, *J* 8.8Hz, H5; 7.27, 1H, d, *J* 8.8Hz, H4; 7.30 5H, m, Ph. Mass spectrum *m/z* 458 (1.9%), 456 (M, 4.6), 425 (1.6), 365 (3.1), 199 (49.0), 91 (100.0).

3-Chloro-2'-hydroxy-2,3',6,6'-tetramethoxy-4'-methylbenzophenone **(5-36)**

A solution of 2'-benzyloxy-3-chloro-2,3',6,6'-tetramethoxy-4'-methylbenzophenone **(5-35)** (0.19 g, 0.42 mmol) in ethyl acetate (7 ml) containing 10% palladium-on-carbon (25 mg) was stirred in an atmosphere of hydrogen for 16 h. The catalyst was then filtered and the solvent was evaporated. The benzophenone so obtained was purified by radial chromatography (SiO_2) using 16-20% ethyl acetate / light petroleum as eluant. The major band yielded *3-chloro-2'-hydroxy-2,3',6,6'-tetramethoxy-4'-methylbenzophenone* **(5-36)** (0.15 g, 98%) as yellow oil (Found: mol. wt. 366.0870. $C_{18}H_{19}O_6{}^{35}Cl$ requires: mol. wt. 366.0870). ^1H n.m.r. ($CDCl_3$) δ 2.31, 3H, s, ArMe; 3.72, 3.76 and 3.90, each 3H, s, OMe; 6.04, 1H, s, H5'; 6.62, 1H, d, *J* 9Hz, H5; 7.29, 1H, d, *J* 9Hz, H4; 13.16, 1H, s, OH. Mass spectrum *m/z* 368 (6.2%), 366 (M, 19.1), 337 (8.54), 335 (25.3), 194 (100.0).

*4-Chloro-1,5,8-trimethoxy-6-methyl-9*H*-xanthen-9-one* **(5-38)**

A solution of 3-chloro-2'-hydroxy-2,3',6,6'-tetramethoxy-4'-methylbenzophenone **(5-36)** (0.3 g, 0.82 mmol) in 1% ethanolic potassium hydroxide (10 ml) was refluxed for 1.7 h in an atmosphere of nitrogen. The cooled mixture was poured into ice-hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, brine and then dried ($MgSO_4$). After removed the solvent the residue was separated by radial chromatography (SiO_2) using 5-50% ethyl acetate / light petroleum as eluant. The faster moving band contained unchanged starting material (200 mg) while the slower band gave *4-chloro-1,5,8-trimethoxy-6-methyl-9*H*-xanthen-9-one* **(5-38)** (70 mg, 25%) which crystallized from the eluant as pale yellow crystals, m.p. 197-199° (Found: C, 61.2; H, 4.5; Cl, 10.4. $C_{17}H_{15}O_5Cl$ requires: C, 61.0; H, 4.5; Cl, 10.6%). ^1H n.m.r. [$(CD_3)_2CO$] δ 2.37, 3H, s, Me; 3.87, 3.93 and 4.00, each 3H,

s, OMe; 6.77, 1H, s, H7; 6.94, 1H, d, *J* 9Hz, H4; 7.72, 1H, d, *J* 9Hz, H3. Mass spectrum *m/z* 336 (2.9%), 334 (M, 10.0), 319 (11.2), 149 (13.0), 43 (100.0)

*4-Chloro-1-hydroxy-5,8-dimethoxy-6-methyl-9*H*-xanthen-9-one (2-Dechloro-8-O-methylthiomelin)* **(5-3)** *and 4-Chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9*H*-xanthen-9-one* **(5-66)**

A solution of boron trichloride (1.25 mmol) in dichloromethane (1 ml) was added to a stirred solution of 4-chloro-1,5,8-trimethoxy-6-methyl-9*H*-xanthen-9-one **(5-38)** (70 mg, 0.21 mmol) in anhydrous dichloromethane (5 ml) at 0° and the stirring continued at 0° for 0.5 h. The solvent was then removed and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with water, brine and dried ($MgSO_4$). After the removal of the solvent the crude product was crystallized from ethyl acetate to give *4-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9*H*-xanthen-9-one* **(5-66)** (20 mg, 30%) as yellow crystals, m.p. 222-224° (Found: mol. wt. 320.0450. $C_{16}H_{13}O_5{}^{35}Cl$ requires: mol. wt. 320.0452). ^{1}H n.m.r. ($CDCl_3$) δ 2.39, 3H, s, ArMe; 4.02 and 4.04, each 3H, s, OMe; 6.62, 1H, s, H7; 6.79, 1H, d, *J* 9Hz, H4; 7.72, 1H, d, *J* 9Hz, H3; 12.39, 1H, s, OH. Mass spectrum *m/z* 322 (14.5%), 320 (M, 39.0), 306 (33.9), 305 (100.0).

The mother liquor was separated by radial chromatography (SiO_2) using 0-10% ethyl acetate / dichloromethane as eluant. The faster moving band yielded 4-chloro-1-hydroxy-5,8-dimethoxy-6-methyl-9*H*-xanthen-9-one **(5-3)** (20 mg, 30%) as yellow crystals, m.p. 224-225° (Found: mol. wt. 320.0450. $C_{16}H_{13}O_5{}^{35}Cl$ requires: mol. wt. 320.0452). ^{1}H n.m.r. ($CDCl_3$) δ 2.45, 3H, s, ArMe; 4.01 and 4.04, each 3H, s, OMe; 6.64, 1H, s, H7; 6.75, 1H, d, *J* 9Hz, H4; 7.59, 1H, d, *J* 9Hz, H3; 13.03, 1H, s, OH. Mass spectrum *m/z* 322 (35.1%), 320 (M, 91.4), 305 (61.5), 304 (37.8), 303 (20.4), 302 (100.0). Standard t.l.c. R_F values: R_F (A) 0.65; R_F (B) 0.45; R_F (C) 0.53; R_F (E)

0.35. Standard h.p.l.c. RI value: 0.81. This synthetic sample was found to be identical (t.l.c., h.p.l.c., ^{1}H n.m.r., m.s.) with the natural material isolated from *Rinodina thiomela.*

The slower moving band afforded a further quantity of 4-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9*H*-xanthen-9-one **(5-66)** (20 mg, 30%, overall yield: 40 mg, 60%).

ii. Using a Friedel-Crafts Method

Methyl 2-Benzyloxy-3-chloro-6-methoxybenzoate **(5-40)**

A mixture of methyl 3-chloro-2-hydroxy-6-methoxybenzoate **(5-39)** (see **iii.**) (1.9 g, 8.8 mmol), benzyl bromide (1.3 ml, 10.9 mmol) and potassium carbonate (2 g, 14.5 mmol) in anhydrous acetone (50 ml) was refluxed for 17 h. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ether. The ether extract was washed with water, brine and then dried ($MgSO_4$). After removal of the solvent the crude product was crystallized from cyclohexane to give *methyl 2-benzyloxy-3-chloro-6-methoxybenzoate* **(5-40)** (2.5 g, 95%) as colourless needles, m.p. 97-99° (Found: C, 63.0; H, 4.8; Cl, 11.6. $C_{16}H_{15}O_4Cl$ requires: C, 62.7; H, 4.9; Cl, 11.6%). ^{1}H n.m.r. ($CDCl_3$) δ 3.81, 6H, s, OMe and CO_2Me; 5.06, 2H, s, $PhCH_2$; 6.67, 1H, d, *J* 8.8Hz, H3; 7.31, 1H, d, *J* 8.8Hz, H4; 7.33-7.42, 5H, m, C_6H_5. Mass spectrum *m/z* 308 (0.2%), 306 (M, 0.7), 91 (100.0)

2-Benzyloxy-3-chloro-6-methoxybenzoic Acid **(5-41)**

A mixture of methyl 2-benzyloxy-3-chloro-6-methoxybenzoate **(5-40)** (3 g, 9.8 mmol), potassium hydroxide (2.5 g), water (20 ml), and dimethyl sulfoxide (60 ml) was

stirred at 100° for 2 h in an atmosphere of nitrogen. The cooled reaction mixture was poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ethyl acetate. The organic extract was washed with water, brine and then dried ($MgSO_4$). The crude product obtained on evaporation of the solvent was crystallized from cyclohexane / ethyl acetate to give *2-benzyloxy-3-chloro-6-methoxybenzoic acid* **(5-41)** (2.5 g, 87%) as colourless prisms, m.p. 162-164° (Found: mol. wt. 292.0503. $C_{15}H_{13}O_4{}^{35}Cl$ requires: mol. wt. 292.0502). ^1H n.m.r. [$(CD_3)_2CO$] δ 3.86, 3H, s, Me; 5.08, 2H, s, CH_2Ph; 6.87, 1H, d, *J* 8.8Hz, 7.29-7.49, 5H, m, H4 and Ph. Mass spectrum *m/z* 294 (0.4%), 292 (M, 1.2), 186 (2.4), 184 (7.3), 91 (100.0)

Ethyl 2-Hydroxy-4-methoxy-6-methylbenzoate **(5-42)**

A mixture of ethyl 2,4-dihydroxy-6-methylbenzoate (ethyl orsellinate) **(2-6)** (19.6 g, 0.1 mol), dimethyl sulfate (10.4 ml, 0.11 mol) and potassium carbonate (34.5 g, 0.25 mol) in anhydrous acetone (200 ml) was refluxed for 14 h. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ether. The ether extract was washed with water, brine and then dried ($MgSO_4$). The crude product obtained on removal of the solvent was purified by column chromatography (SiO_2) using 3-15% ethyl acetate / light petroleum as eluant. The major band afforded ethyl 2-hydroxy-4-methoxy-6-methylbenzoate **(5-42)** (16 g, 76%) which crystallized from the eluant as colourless needles, m.p. 74-77° (lit.[129] m.p. 76°). ^1H n.m.r. ($CDCl_3$) δ 1.40, 3H, t, *J* 7Hz, CH_2CH_3; 2.51, 3H, s, ArMe; 3.79, 3H, s, OMe; 4.40, 2H, q, *J* 7Hz, CH_2CH_3; 6.25, 1H, d, *J* 2Hz, H3; 6.33, 1H, d, *J* 2Hz, H5; 11.79, 1H, s, OH.

Ethyl 5-Bromo-2-hydroxy-4-methoxy-6-methylbenzoate **(5-43)**

Bromine (3.26 g, 20.4 mmol) in carbon tetrachloride (200 ml) was added dropwise to a stirred solution of ethyl 2-hydroxy-4-methoxy-6-methylbenzoate (**5-42**) (4 g, 19.1 mmol) in carbon tetrachloride (250 ml) at -15° over 10 min. Dilute potassium hydrogen carbonate solution was added to the mixture and the organic layer was washed with water, brine and dried ($MgSO_4$). After the solvent was removed the crude product was purified by radial chromatography using 3-20% ethyl acetate / light petroleum as eluant. The major band yielded ethyl 5-bromo-2-hydroxy-4-methoxy-6-methylbenzoate (**5-43**) (5 g, 91%) which crystallized from the solvent as long colourless needles, m.p. 113-114° (lit.[17] m.p. 112-113°) (Found: C, 46.2; H, 4.6; Br, 27.5%. $C_{11}H_{13}O_4Br$ requires: C, 45.7; H, 4.5; Br, 27.6%). ^1H n.m.r. ($CDCl_3$) δ 1.42, 3H, t, *J* 7Hz, CH_2CH_3; 2.70, 3H, s, ArMe; 3.89, 3H, s, OMe; 4.43, 2H, q, *J* 7Hz, CH_2CH_3; 6.40, 1H, s, ArH, 11.55, 1H, s, OH. Mass spectrum *m/z* 290 (37.2%), 288 (M, 37.5), 245 (67.2), 242 (70.7), 63 (100).

Ethyl 2-Benzyloxy-5-bromo-4-methoxy-6-methylbenzoate **(5-44)**

A mixture of ethyl 5-bromo-2-hydroxy-4-methoxy-6-methylbenzoate (**5-43**) (13 g, 45 mmol), benzyl bromide (5.8 ml, 49 mmol) and potassium carbonate (13.8 g, 100 mmol) in anhydrous acetone (170 ml) was refluxed for 16 h. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ether. The ether extract was washed with water, brine and then dried ($MgSO_4$). The crude product obtained on removal of the solvent was purified by column chromatography (SiO_2) using 5-12% ethyl acetate / light petroleum as eluant. The major band afforded *ethyl 2-benzyloxy-5-bromo-4-methoxy-6-methylbenzoate* (**5-44**) (14 g, 82%) as yellow oil (Found: mol. wt. 378.0467. $C_{18}H_{19}O_4{}^{79}Br$ requires: mol. wt. 378.0467). ^1H n.m.r. ($CDCl_3$) δ 1.30, 3H, t, *J* 7Hz, CH_2CH_3; 2.37, 3H, s, ArMe;

3.82, 3H, s, OMe; 4.35, 2H, q, *J* 7Hz, CH_2CH_3; 5.10, 2H, s, CH_2Ph; 6.38, 1H, s, ArH; 7.35, 5H, m, Ph. Mass spectrum *m/z* 380 (1.2%), 378 (M, 1.3), 244 (1.4), 242 (1.4), 91 (100.0).

2-Benzyloxy-5-bromo-4-methoxy-6-methylbenzyl Alcohol **(5-45)**

Ethyl 2-benzyloxy-5-bromo-4-methoxy-6-methylbenzoate **(5-44)** (11.5 g, 30 mmol) in anhydrous ether (130 ml) was added dropwise to a suspension of lithium aluminium hydride (3.5 g, 92 mmol) in anhydrous ether (50 ml) and the mixture was refluxed for 1.5 h. Hydrochloric acid (4 M, 60 ml) was then added dropwise to the mixture at 0°. The organic layer was washed with water and brine, and then dried ($MgSO_4$). The residue obtained on removal of the solvent was crystallized from cyclohexane to give *2-benzyloxy-5-bromo-4-methoxy-6-methylbenzyl alcohol* **(5-45)** (9 g, 88%) as colourless crystals, m.p. 111-112° (Found: mol. wt. 336.0360. $C_{16}H_{17}O_3{}^{79}Br$ requires: mol. wt. 336.0361). ^1H n.m.r. ($CDCl_3$) δ 2.51, 3H, s, ArMe; 3.84, 3H, s, OMe; 4.78, 2H, s, CH_2OH; 5.11, 2H, s, CH_2Ph; 6.45, 1H, s, ArH; 7.39, 5H, m, Ph. Mass spectrum *m/z* 338 (1.7%), 336 (M,1.6), 230 (13.1), 228 (13.0), 138 (2.2), 91 (100.0).

2-Benzyloxy-5-bromo-4-methoxy-6-methylbenzaldehyde **(5-46)**

Activated manganese dioxide[62] (34 g) was added to a solution of 2-benzyloxy-5-bromo-4-methoxy-6-methylbenzyl alcohol **(5-45)** (9 g, 26.7 mmol) in dichloromethane (100 ml) and chloroform (100 ml) and the mixture was gently refluxed. More activative manganese dioxide (10 g and 5 g) was added to the above mixture after it was refluxed for 10 h and 33 h respectively, and refluxing continued for a total of 50 h. After cooling the solid was filtered and washed three times with dichloromethane. The

combined filtrate was dried ($MgSO_4$) and the crude product obtained after removal of the solvent was separated by radial chromatography (SiO_2) using 7-40% ethyl acetate / light petroleum as eluant. The major band afforded *2-benzyloxy-5-bromo-4-methoxy-6-methylbenzaldehyde* **(5-46)** (8 g, 89%) which crystallized from ethyl acetate / light petroleum as colourless prisms, m.p. 79-80° (Found: mol. wt. 334.0203. $C_{16}H_{15}O_3{}^{79}Br$ requires: mol. wt. 334.0205). ^1H n.m.r. ($CDCl_3$) δ 2.72, 3H, s, ArMe; 3.89, 3H, s, OMe; 5.17, 2H, s, CH_2Ph; 6.43, 1H, s, ArH; 7.38, 5H, m, Ph; 10.52, 1H, s, CHO. Mass spectrum *m/z* 336 (0.6%), 334 (M, 0.5), 245 (0.6), 244 (0.7), 243 (0.6), 242 (0.6), 91 (100.0).

2-Benzyloxy-5-bromo-4-methoxy-6-methylphenol **(5-47)**

A solution of 2-benzyloxy-5-bromo-4-methoxy-6-methylbenzaldehyde **(5-46)** (8.5 g, 25.4 mmol) in anhydrous dichloromethane (100 ml) was added over 30 min to a stirred solution of 50-60% *m*-chloroperbenzoic acid (21 g, 60 mmol) in anhydrous dichloromethane (300 ml) at room temperature. The solution was stirred for a further 16 h at this temperature and then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed with potassium hydrogen carbonate until effervescence ceased, and then with saturated brine. Removal of the solvent gave the crude formate.

Aqueous potassium hydroxide (10%, 100 ml) was added to a solution of the crude formate in methanol (150 ml) at 0° in a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 2.5 h, then poured into cold, dilute hydrochloric acid and was extracted with ether. The organic extract was washed twice with saturated potassium hydrogen carbonate, water, brine and then dried ($MgSO_4$). After removal of solvent the residue was purified by radial chromatography (SiO_2) using 3-5% ethyl acetate / light petroleum as eluant. The major band afforded *2-benzyloxy-5-bromo-4-*

methoxy-6-methylphenol (**5-47**) (7 g, 85%) which crystallized from the eluant as colourless prisms, m.p. 142-143° (Found: C, 55.3; H, 4.7. $C_{15}H_{15}O_3Br$ requires: C, 55.8; H, 4.7%). ^1H n.m.r. ($CDCl_3$) δ 2.29, 3H, s, ArMe; 3.80, 3H, s, OMe; 5.08, 2H, s, CH_2Ph; 6.49, 1H, s, ArH; 7.35, 5H, m, Ph; 8.25, 1H, s, OH. Mass spectrum *m/z* 324 (0.6%), 322 (M, 0.6), 243 (1.1), 205 (1.2), 203 (1.1), 91 (100.0).

3-Benzyloxy-6-bromo-2,5-dimethoxytoluene (**5-48**)

A mixture of 2-benzyloxy-5-bromo-4-methoxy-6-methylphenol (**5-47**) (7 g, 21.7 mmol), dimethyl sulfate (3.1 ml, 33 mmol) and potassium carbonate (6 g, 43 mmol) in anhydrous acetone (150 ml) was refluxed for 19 h. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ether. The ether extract was washed with water and brine and then dried ($MgSO_4$). The crude product obtained on removal of the solvent was separated by column chromatography (SiO_2) using 3-8% ethyl acetate / light petroleum as eluant. The major band afforded *3-benzyloxy-6-bromo-2,5-dimethoxytoluene* (**5-48**) (3.8 g, 52%) as colourless oil (Found: C, 57.0; H, 5.3; Br, 23.9. $C_{16}H_{17}O_3Br$ requires: C, 57.0; H, 5.1; Br, 23.7%). ^1H n.m.r. ($CDCl_3$) δ 2.37, 3H, s, ArMe; 3.78, 6H, s, OMe; 5.11, 2H, s, CH_2Ph; 6.47, 1H, s, ArH; 7.39, 5H, m, Ph. Mass spectrum *m/z* 338 (1.5%), 336 (M, 1.5), 257 (2.5), 247 (2.9), 245 (2.8), 91 (100.0).

Attempted Acylation of 3-Benzyloxy-6-bromo-2,5-dimethoxytoluene (**5-48**) *with 2-Benzyloxy-3-chloro-6-methoxybenzoic Acid* (**5-41**)

A mixture of 3-benzyloxy-6-bromo-2,5-dimethoxytoluene (**5-48**) (1.36 g, 4.03 mmol), 2-benzyloxy-3-chloro-6-methoxybenzoic acid (**5-41**) (0.80 g, 2.74 mmol) and trifluoroacetic anhydride (7 ml) in anhydrous 2,2-dichloroethane (20 ml) was refluxed

for 2 days. Further trifluoroacetic anhydride (12 ml) was added and the mixture was refluxed for a further 5 days. T.l.c. examination showed no trace of the required depside formed in the mixture.

iii. Using a Smiles Rearrangement

Methyl 2,6-dimethoxybenzoate **(5-52)**

A mixture of 2,6-dihydroxybenzoic acid **(5-5)** (15.3 g, 0.099 mol), dimethyl sulfate (35 ml, 0.369 mol) and potassium carbonate (55 g, 0.4 mol) in anhydrous acetone (300 ml) was refluxed for 20 h. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ether. The ether extract was washed with water, brine and then dried ($MgSO_4$). The residue obtained on removal of the solvent was crystallized from hexane to give the product **(5-52)** (15 g, 77%) as colourless prisms, m.p. 73-78° (lit.[86] m.p. 88°). ^1H n.m.r. ($CDCl_3$) δ 3.81, 6H, s, OMe; 3.90, 3H, s, CO_2Me; 6.55, 2H, d, *J* 8.8Hz, H3 and H5; 7.28, 1H, t, *J* 8.8Hz, H4. Mass spectrum *m/z* 196 (M, 20.0%), 165 (100.0), 150 (20).

Methyl 2-hydroxy-6-methoxybenzoate **(5-53)**

A solution of boron trichloride (19 g, 0.16 mol) in dichloromethane (50 ml) was added dropwise over 40 min to a stirred solution of methyl 2,6-dimethoxybenzoate **(5-52)** (6.5 g, 0.033 mol) in anhydrous dichloromethane (70 ml) at -10°. The mixture was stirred at 0° for 0.5 h, and then the solvent was removed and the residue dissolved in ethyl acetate. The organic solution was washed with water, brine and then dried ($MgSO_4$). Removal of the solvent yielded the product **(5-53)** (5.9 g, 98%) as a yellow oil, b.p. 130-135° / 10 mm (lit.[24] b.p. 134-138° / 9 mm). ^1H n.m.r. ($CDCl_3$) δ 3.85,

3H, s, OMe; 3.94, 3H, s, CO_2Me; 6.40, 1H, d, *J* 8Hz, H3; 6.58, 1H, d, *J* 8Hz, H5; 7.32, 1H, t, *J* 8Hz, H4; 11.45, 1H, b, OH. Mass spectrum *m/z* 182 (M, 22.3%), 151 (25.8), 150 (100.0).

Methyl 3-Chloro-2-hydroxy-6-methoxybenzoate **(5-39)** *and Methyl 3-Chloro-6-hydroxy-2-methoxybenzoate* **(5-54)**

A solution of sulfuryl chloride (2.9 ml, 35 mmol) in anhydrous ether (80 ml) was added dropwise to a stirred solution of methyl 2-hydroxy-6-methoxybenzoate (**5-53**) (5.9 g, 32 mmol) in anhydrous ether (200 ml) over a period of 30 min, and stirring continued for 22 h at room temperature. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ether. The ether extract was washed with water, brine and then dried ($MgSO_4$). The crude product obtained on removal of the solvent was separated by column chromatography (SiO_2) using 2-8% ethyl acetate / light petroleun as eluant. The faster moving band yielded *methyl 3-chloro-6-hydroxy-2-methoxybenzoate* **(5-54)** (2 g, 29%) which crystallized from the eluant as colourless needles, m.p. 37-40° (Found: mol.wt. 216.0188. $C_9H_9O_4{}^{35}Cl$ requires: mol. wt. 216.0189). ^1H n.m.r. ($CDCl_3$) δ 3.86, 3H, s, CO_2Me; 4.01, 3H, s, OMe; 6.74, 1H, d, *J* 8.8Hz, H5; 7.42, 1H, d, *J* 8.8Hz, H4; 11.09, 1H, s, OH. Mass spectrum *m/z* 218 (7.9%), 216 (M, 22.3), 186 (29.2), 184 (100.0).

The slower moving band gave *methyl 3-chloro-2-hydroxy-6-methoxybenzoate* **(5-39)** (1.4 g, 20%) which crystallized from the eluant as colourless needles, m.p. 84-85° (Found: C, 50.1; H, 4.1; Cl, 16.1. $C_9H_9O_4Cl$ requires: C, 49.9; H, 4.2; Cl, 16.4%). ^1H n.m.r. ($CDCl_3$) δ 3.84, 3H, s, CO_2Me; 3.96, 3H, s, OMe; 6.38, 1H, d, *J* 8.8Hz, H3; 7.40, 1H, d, *J* 8.8Hz, H4; 12.01, 1H, b, OH. Mass spectrum *m/z* 218 (4.3%), 216 (M, 11.9), 186 (30.2), 184 (100.0)

Methyl 2-Acetyl-3-chloro-6-methoxybenzoate **(5-60)**

A solution of methyl 3-chloro-2-hydroxy-6-methoxybenzoate **(5-39)** (74 mg, 0.34 mmol), acetic anhydride (1.2 ml) and concentrated sulphuric acid (1 drop) was stirred at room temperature for 19 h. Water (10 ml) was added and the mixture stirred at room temperature for a further 3 h. The mixture was then extrated with ether and the ethereal layer washed with water, brine and then dried ($MgSO_4$). After the removal of solvent the crude product was purified by radial chromatography (SiO_2) using 15-60% ethyl acetate / light petroleum as eluant. The major band afforded *methyl 2-acetyl-3-chloro-6-methoxybenzoate* **(5-60)** (50 mg, 57%) which crystallized from the eluant as colourless crystals, m.p. 108-109° (Found: C,51.5; H, 4.3; Cl, 13.7. $C_{11}H_{11}O_5Cl$ requries: C, 51.1; H, 4.3; Cl, 13.7%). ^1H n.m.r. ($CDCl_3$) δ 2.29, 3H, s, Ac; 3.83 and 3.88, each 3H, s, OMe; 6.78, 1H, d, *J* 9Hz, H3; 7.42, 1H, d, *J* 9Hz, H4. Mass spectrum *m/z* 260 (0.5%), 258 (M, 1.5), 229 (1.3), 216 (23.9), 186 (30.8), 184 (100.0).

Methyl 6-Acetoxy-3-chloro-2-methoxybenzoate **(5-61)**

A solution of methyl 3-chloro-6-hydroxy-2-methoxybenzoate **(5-54)** (15 mg, 0.07 mmol), acetic anhydride (0.8 ml) and concentrated sulphuric acid (1 drop) was stirred at room temperature for 19 h. Water (10 ml) was then added and the mixture stirred at room temperature for a further 3 h. The mixture was extrated with ether and the ethereal layer washed with water, brine and then dried ($MgSO_4$). The crude product obtained on removal of solvent was purified by preparative t.l.c. (SiO_2) using 25% ethyl acetate / light petroleum as eluant. The major band afforded *methyl 6-acetyl-3-chloro-2-methoxybenzoate* **(5-61)** (10 mg, 55%) as a colourless oil (Found: mol. wt. 258.0296. $C_{11}H_{11}O_5{}^{35}Cl$ requires: mol. wt. 258.0295). ^1H n.m.r. ($CDCl_3$) δ 2.25, 3H, s, Ac; 3.91 and 3.92, each 3H, s, OMe; 6.89, 1H, d, *J* 9Hz, H5; 7.45, 1H, d, *J* 9Hz, H4.

Mass spectrum *m/z* 260 (0.2%), 258 (M, 0.6), 229 (0.8), 227 (2.6), 218 (9.4), 217 (2.9), 216 (29.4), 186 (32.4), 184 (100.0).

3-Chloro-2-hydroxy-6-methoxybenzoic Acid **(5-55)**

A solution of methyl 3-chloro-2-hydroxy-6-methoxybenzoate **(5-39)** (0.65 g, 3 mmol), potassium hydroxide (0.7 g), dimethyl sulfoxide (17 ml) and water (5 ml) was heated at 90-100° for 4 h in an atmosphere of nitrogen. The cooled mixture was poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ethyl acetate. The organic extract was washed with water, brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was crystallized from cyclohexane / ethyl acetate to give *3-chloro-2-hydroxy-6-methoxybenzoic acid* **(5-55)** (0.5 g, 83%) as colourless prisms, m.p. 126° (Found: mol. wt. 202.0033. $C_8H_7O_4{}^{35}Cl$ requires: mol. wt. 202.0033). ^1H n.m.r. [$(CD_3)_2CO$] δ 4.14, 3H, s, OMe; 6.77, 1H, d, *J* 9Hz, H5; 7.62, 1H, d, *J* 9Hz, H4; 12.79, 1H, s, OH. Mass spectrum *m/z* 204 (3.4%), 202 (M, 10.7), 186 (32.0), 184 (100.0).

Ethyl 4-Benzyloxy-3,6-dihydroxy-2-methylbenzoate **(5-57)**

A saturated solution of potassium persulphate (5.9 g, 22 mmol) in water (450 ml) was added dropwise over 45 min to a stirred solution of ethyl 4-benzyloxy-2-hydroxy-6-methylbenzoate **(2-7)** (5.5 g, 19 mmol) in 20% aqueous sodium hydroxide (44 ml) and dioxane (55ml) in an atmosphere of nitrogen. The temperature of the reaction mixture was maintained well below 5° throughout the addition. After the mixture was stirred at room temperature for 17 h it was acidified to pH 6 by addition of concentrated hydrochloric acid. Unreacted starting material was then extracted with ether. A further quantity of concentrated hydrochloric acid (35 ml) and solid sodium

sulfite (4 g) was then added to the aqueous layer and the mixture was stirred and warmed to 80° for 1.5 h in an atmosphere of nitrogen. The cooled mixture was extracted with ether and the ethereal layer washed with water, brine and then dried ($MgSO_4$). Removing the solvent yielded the product **(5-57)** (4 g, 70%) which crystallized from cyclohexane as pale pink crystals, m.p. 110-113° (lit.[30] m.p. 106-108°). ^1H n.m.r. ($CDCl_3$) δ 1.41, 3H, t, *J* 7Hz, CH_2CH_3; 2.46, 3H, s, ArMe, 4.40, 2H, q, *J* 7Hz, CH_2CH_3; 5.11, 2H, s, CH_2Ph; 6.44, 1H, s, ArH; 7.39, 5H, m, Ph; 11.33, 1H, b, OH.

Ethyl 4-Benzyloxy-3,6-dimethoxy-2-methylbenzoate **(5-58)**

A mixture of ethyl 4-benzyloxy-3,6-dihydroxy-2-methylbenzoate **(5-57)** (2.2 g, 7.3 mmol), dimethyl sulfate (2 ml, 21.2 mmol) and potassium carbonate (5 g, 36 mmol) in anhydrous acetone (25 ml) was heated under reflux for 18 h in an atmosphere of nitrogen. The mixture was then poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ether. The ether extract was washed with water, brine and then dried ($MgSO_4$). Removal of the solvent yielded the crude product which was purified by column chromatography (SiO_2) using 5-20% ethyl acetate / light petroleum as eluant. The major band afforded ethyl 4-benzyloxy-3,6-dimethoxy-2-methylbenzoate[30] **(5-58)** (2.3 g, 97%) as colourless oil. ^1H n.m.r. ($CDCl_3$) δ 1.35, 3H, t, *J* 7Hz, CH_2CH_3; 2.22, 3H, s, ArMe; 3.71 and 3.76, each 3H, s, OMe; 4.36, 2H, q, *J* 7Hz, CH_2CH_3; 5.12, 2H, s, CH_2Ph; 6.40, 1H, s, ArH; 7.38, 5H, m, Ph.

Ethyl 4,6-Dihydroxy-3-methoxy-2-methylbenzoate **(5-59)**

A solution of boron trichloride (70 mmol) in dichloromethane (13 ml) was added dropwise to a stirred solution of ethyl 4-benzyloxy-3,6-dimethoxy-2-methylbenzoate (**5-**

58) (3.8 g, 11.6 mmol) in anhydrous dichloromethane (50 ml) at 0° and stirring was continued at 0° for 15 min. Water was then added, the solvent removed under reduced pressure and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with water, brine and then dried ($MgSO_4$). After the removal of the solvent the crude product was purified by column chromatography (SiO_2) using 2.5-20% ethyl acetate / light petroleum as eluant. The major band afforded ethyl 4,6-dihydroxy-3-methoxy-2-methylbenzoate **(5-59)** (2.5 g, 95%) which crystallized from the eluant as colourless fine needles, m.p. 89-91° (lit.[36] m.p. 87°) (Found: C, 58.1; H, 6.4. $C_{11}H_{14}O_5$ requires: C, 58.4; H, 6.2%). ^{1}H n.m.r. ($CDCl_3$) δ 1.43, 3H, t, *J* 7Hz, CH_2CH_3; 2.48, 3H, s, ArMe; 3.71, 3H, s, OMe; 4.41, 2H, q, *J* 7Hz, CH_2CH_3; 6.43, 1H, s, ArH; 11.57, 1H, s, OH. Mass spectrum *m/z* 226 (M, 22.4%), 211 (1.7), 180 (100.0).

Ethyl 4-(3'-Chloro-2'-hydroxy-6'-methoxybenzoyloxy)-6-hydroxy-3-methoxy-2-methylbenzoate **(5-63)**

A mixture of 3-chloro-2-hydroxy-6-methoxybenzoic acid **(5-55)** (0.32 g, 1.6 mmol), ethyl 4,6-dihydroxy-3-methoxy-2-methylbenzoate **(5-59)** (0.36 g, 1.6 mmol), and *N,N*-dicyclohexylcarbodiimide (0.65 g, 3.2 mmol) in toluene (5 ml), and anhydrous ether (6 ml) was stirred at room temperature for 24 h. The precipitate was then filtered and washed with ethyl acetate. The combined filtrate was evaporated and the residue was purified by column chromatography (SiO_2) using 5-30% ethyl acetate / light petroleum as eluant. The major band afforded *ethyl 4-(3'-chloro-2'-hydroxy-6'-methoxybenzoyloxy)-6-hydroxy-3-methoxy-2-methylbenzoate* **(5-63)** (0.2 g, 30%) as yellow gum (Found: mol. wt. 410.0768. $C_{19}H_{19}O_8{}^{35}Cl$ requires: mol. wt. 410.0768). ^{1}H n.m.r. ($CDCl_3$) δ 1.45, 3H, t, *J* 7Hz, CH_2CH_3; 2.54, 3H, s, ArMe; 3.68 and 3.91, each 3H, s, OMe; 4.46, 2H, q, *J* 7Hz, CH_2CH_3; 6.51, 1H, d, *J* 9Hz, H5'; 6.75, 1H,

s, H5; 7.56, 1H, d, *J* 9Hz, H4'; 11.30 and 11.53, each 1H, s, OH. Mass spectrum *m/z* 410 (M, 0.15%), 316 (0.9), 228 (7.6), 226 (16.8), 186 (31.5), 184 (100.0).

3-Chloro-2-(4'-ethoxycarbonyl-5'-hydroxy-2'-methoxy-3'-methylphenoxy)-6-methoxybenzoic Acid **(5-64)**

A solution of ethyl 4-(3'-chloro-2'-hydroxy-6'-methoxybenzoyloxy)-5-hydroxy-3-methoxy-2-methylbenzoate **(5-63)** (90 mg, 0.22 mmol) and anhydrous potassium carbonate (0.1 g, 0.7 mmol) in anhydrous dimethyl sulfoxide (10 ml) was heated at 75-80° in an atmosphere of nitrogen for 16 h. The reaction mixture was then acidified with excess cold dilute hydrochloric acid, extracted with ethyl acetate, and the ethyl acetate extract washed with water, brine and then dried ($MgSO_4$). The crude product obtained on evaporation of the solvent was purified by preparative t.l.c. (SiO_2) using 25% ethyl acetate / light petroleum to give *3-chloro-2-(4'-ethoxycarbonyl-5'-hydroxy-2'-methoxy-3'-methylphenoxy)-6-methoxybenzoic acid* **(5-64)** (60 mg, 67%) as yellow gum (Found: mol. wt. 410.0768. $C_{19}H_{19}O_8{}^{35}Cl$ requires: mol. wt. 410.0768). ^1H n.m.r. ($CDCl_3$) δ 1.42, 3H, t, *J* 7Hz, $CH_2\mathbf{CH_3}$; 2.53, 3H, s, ArMe; 3.83 and 3.95, each 3H, s, OMe; 4.39, 2H, q, *J* 7Hz, $\mathbf{CH_2}CH_3$; 5.93, 1H, s, H6'; 6.89, 1H, d, *J* 9Hz, H5; 7.53, 1H, d, *J* 9Hz, H4; 11.46, 1H, s, OH.

Ethyl 4-Chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9-oxo-9H-xanthen-7-carboxylate **(5-65)**

The foregoing carboxylic acid **(5-64)** (60 mg, 0.15 mmol) was dried by azeotropic distillation with toluene and then dissolved in anhydrous toluene (2 ml) and trifluoroacetic anhydride (0.6 ml) added and the mixture was stirred at room temperature for 17 h. The mixture was then diluted with ethyl acetate and washed with water, brine

and then dried ($MgSO_4$). The residue obtained after removal of solvent was purified by radial chromatography (SiO_2) to give *ethyl 4-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9-oxo-9*H*-xanthen-7-carboxylate* **(5-65)** (40 mg, 68%) as yellow oil (Found: mol. wt. 392.0661. $C_{19}H_{17}O_7{}^{35}Cl$ requires: mol. wt. 392.0663). ^{1}H n.m.r. ($CDCl_3$) δ 1.41, 3H, t, *J* 7Hz, CH_2CH_3; 2.38, 3H, s, ArMe; 3.99 and 4.02, each 3H, s, OMe; 4.45, 2H, q, *J* 7Hz, CH_2CH_3; 6.79, 1H, d, *J* 9Hz, H4; 7.72, 1H, d, *J* 9Hz, H3; 12.79, 1H, s, OH. Mass spectrum *m/z* 394 (15.3%), 392 (M, 43.1), 358 (11.1), 348 (13.5), 347 (17.8), 346 (16.3), 333 (29.8), 331 (53.3), 67 (100.0).

*4-Chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9*H*-xanthen-9-one* **(5-66)**

A mixture of ethyl 4-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9-oxo-9*H*-xanthen-7-carboxylate **(5-65)** (50 mg, 0.13 mmol), potassium hydroxide (0.1 g), dimethyl sulfoxide (15 ml) and water (3 ml) was heated at 140° for 2 h in an atmosphere of nitrogen. The cooled mixture was poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ethyl acetate. The organic layer was washed with water, brine and then dried ($MgSO_4$). The crude acid obtained after removal of the solvent was dissolved in anhydrous diglyme (15 ml). Cuprous oxide (0.1 g) and 2,2-bipyridyl (0.6 g) were added and the mixture was stirred at room temperature for 0.5 h and then refluxed for 2.5 h in an atmosphere of nitrogen. The cooled mixture was poured into a mixture of ice and hydrochloric acid and was extracted with ethyl acetate. The organic solution was washed with water and brine, and then dried ($MgSO_4$). After the removal of solvent the residue was purified by preparative t.l.c. (SiO_2) using 25% ethyl acetate / light petroleum as eluant. The major band yielded 4-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9*H*-xanthen-9-one **(5-66)** (15 mg, 36%) which was identical (t.l.c., ^{1}H n.m.r., mass spectrum) with the material prepared in subsection **i.** above.

*4-Chloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthen-9-one* **(5-68)** and *4-Chloro-5,8-dihydroxy-1-methoxy-6-methyl-9*H*-xanthen-9-one* **(5-70)**

Boron tribromide (0.07 ml, 0.73 mmol) was added to a stirred solution of 4-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9*H*-xanthen-9-one **(5-66)** (10 mg, 0.03 mmol) in anhydrous dichloromethane (5 ml) at -10° and stirring continued at -10° for 0.4 h. Water was added and the mixture was diluted with ethyl acetate. The organic extract was washed with water, brine and dried ($MgSO_4$). After the removal of the solvent the crude product was separated by preparative t.l.c. (SiO_2) using 25% ethyl acetate / light petroleum as eluant. The faster moving band gave *4-chloro-1,5,8-trihydroxy-6-methyl-9*H*-xanthen-9-one* **(5-68)** (5 mg, 57%) which crystallized from the eluant as yellow crystals, m.p. 212-214° (Found: mol. wt. 292.0139. $C_{14}H_9O_5{}^{35}Cl$ requires: mol. wt. 292.0139). ^{1}H n.m.r. ($CDCl_3$) δ 2.41, 3H, s, ArMe; 6.67, 1H, s, H7; 6.79, 1H, d, *J* 9Hz, H4; 7.65, 1H, d, *J* 9Hz, H3; 10.80 and 11.92, each 1H, s, OH. Mass spectrum *m/z* 294 (31.2%), 292 (M, 100.0).

The slower band yielded *4-chloro-5,8-dihydroxy-1-methoxy-6-methyl-9*H*-xanthen-9-one* **(5-70)** (4 mg, 43%) which crystallized from the eluant as yellow crystals, m.p. 194-196° (Found: mol. wt. 306.0295. $C_{15}H_{11}O_5{}^{35}Cl$ requires: mol. wt. 306.0295). ^{1}H n.m.r. ($CDCl_3$) δ 2.38, 3H, s, ArMe; 4.03, 3H, s, OMe; 6.62, 1H, s, H7; 6.79, 1H, d, *J* 9Hz, H4; 7.69, 1H, d, *J* 9Hz, H3; 11.85, 1H, s, OH. Mass spectrum *m/z* 308 (8.3%), 306 (M, 25.1), 294 (10.5), 292 (34.1), 288 (29.4), 57 (100.0).

*4-Chloro-1,8-dihydroxy-5-methoxy-6-methyl-9*H*-xanthen-9-one* **(5-69)**

An ethereal solution of diazomethane [prepared[128] from *p*-tolysulfonylmethylnitrosamide (0.4 g)] was added to a solution of 4-chloro-1,5,8-

trihydroxy-6-methyl-9*H*-xanthen-9-one (**5-68**) (0.2 g, 0.68 mmol) in acetone (100 ml) at 0°. The reaction mixture was then stood at room temperature for 5 h. Acetic acid (several drops) was used to destroy the excess diazomethane and the mixture was diluted with ethyl acetate and washed with sodium hydrogen carbonate, brine and then dried ($MgSO_4$). After removal of the solvent the residue was separated by column chromatography (SiO_2) using 4-40% ethyl acetate / light petroleum as eluant. The faster moving band yielded crude product which was washed with light petroleum to give *4-chloro-1,8-dihydroxy-5-methoxy-6-methyl-9*H*-xanthen-9-one* (**5-69**) (15 mg, 7%) as yellow crystals, m.p. 193-194° dec. (Found: mol. wt. 306.0295. $C_{15}H_{11}O_5{}^{35}Cl$ requires: mol. wt. 306.0295). ^1H n.m.r. ($CDCl_3$) δ 2.41, 3H, s, ArMe; 4.02, 3H, s, OMe; 6.67, 1H, s, H7; 6.79, 1H, d, *J* 9Hz, H4; 7.67, 1H, d, *J* 9Hz, H3; 11.28 and 11.90, each 1H, s, OH. Mass spectrum *m/z* 308 (14.1%), 306 (M, 38.9), 293 (32.0), 292 (17.0), 291 (100.0). Subsequent minor bands which eluted from the column contained traces of 4-chloro-1-hydroxy-5,8-dimethoxy-6-methyl-9*H*-xanthen-9-one (**5-3**) and 4-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9*H*-xanthen-9-one (**5-66**) respectively.

6.5.d. Synthesis of 4-Dechlorothiomelin (TH1) and Derivatives

3-Chloro-6-hydroxy-2-methoxybenzoic Acid (**5-56**)

A solution of methyl 3-chloro-6-hydroxy-2-methoxybenzoate (**5-54**) (3.5 g, 16.2 mmol), potassium hydroxide (3.6 g), dimethyl sulfoxide (70 ml) and water (20 ml) was heated at 100-115° for 4.5 h in an atmosphere of nitrogen. The cooled mixture was poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ethyl acetate. The organic solution was washed with water and brine and then dried ($MgSO_4$). The crude product obtained after evaporation of the solvent was crystallized from cyclohexane / ethyl acetate to give *3-chloro-6-hydroxy-2-methoxybenzoic acid* (**5-**

56) (1.3 g, 40%) as short colourless needles, m.p. 128-129° (Found: mol. wt. 202.0033. $C_8H_7O_4{}^{35}Cl$ requires: mol. wt. 202.0033). ^1H n.m.r. [$(CD_3)_2CO$] δ 3.97, 3H, s, OMe; 6.81, 1H, d, *J* 9Hz, H5; 7.56, 1H, d, *J* 9Hz, H4. Mass spectrum *m/z* 204 (5.6%), 202 (M, 16.7), 186 (29.5), 184 (96.6), 143 (32.6), 141 (100.0).

Ethyl 4-(3'-Chloro-6'-hydroxy-2'-methoxybenzoyloxy)-5-hydroxy-3-methoxy-2-methylbenzoate **(5-72)**

A solution of 3-chloro-6-hydroxy-2-methoxybenzoic acid **(5-56)** (0.97 g, 4.8 mmol), ethyl 4,6-dihydroxy-3-methoxy-2-methylbenzoate **(5.59)** (0.90 g, 4.0 mmol), and *N,N*-dicyclohexylcarbodiimide (1.65 g, 8 mmol) in toluene (10 ml), and anhydrous ether (15 ml) was stirred at room temperature for 40 h. The precipitate was then filtered and washed with ethyl acetate. The combined filtrate was evaporated and the residue was purified by radial chromatography (SiO_2) using 2-10% ethyl acetate / hexane as eluant. The major band afforded *ethyl 4-(3'-chloro-6'-hydroxy-2'-methoxybenzoyloxy)-6-hydroxy-3-methoxy-2-methylbenzoate* **(5-72)** (0.32 g, 19%) as yellow oil (Found: mol. wt. 410.0768. $C_{19}H_{19}O_8{}^{35}Cl$ requires: mol. wt. 410.0768). ^1H n.m.r. ($CDCl_3$) δ 1.44, 3H, t, *J* 7Hz, CH_2CH_3; 2.54, 3H, s, ArMe; 3.69 and 3.98, each 3H, s, OMe; 4.47, 2H, q, *J* 7Hz, CH_2CH_3; 6.72, 1H, s, H5; 6.86, 1H, d, *J* 9Hz, H5'; 7.51, 1H, d, *J* 9Hz, H4'; 10.64 and 11.22, each 1H, s, OH. Mass spectrum *m/z* 412 (0.2%), 410 (M, 0.6), 370 (2.2), 368 (3.9), 316 (1.2), 226 (44.6), 186 (27.7), 184 (83.1), 180 (100.0).

3-Chloro-6-(4'-ethoxycarbonyl-5'-hydroxy-2'-methoxy-3'-methylphenoxy)-2-methoxybenzoic Acid **(5-73)**

A solution of ethyl 4-(3'-chloro-6'-hydroxy-2'-methoxybenzoyloxy)-5-hydroxy-3-methoxy-2-methylbenzoate **(5-72)** (0.32 g, 0.78 mmol) and anhydrous potassium carbonate (0.3 g, 2 mmol) in anhydrous dimethyl sulfoxide (10 ml) was heated at 76-85° in an atmosphere of nitrogen for 20 h. The reaction mixture was then acidified with cold dilute hydrochloric acid, extracted with ethyl acetate, and the ethyl acetate extract washed with water, brine and then dried ($MgSO_4$). The crude product obtained after evaporation of the solvent was purified by preparative t.l.c. (SiO_2) using 50% ethyl acetate / hexane as eluant. The major band yielded *3-chloro-6-(4'-ethoxycarbonyl-5'-hydroxy-2'-methoxy-3'-methylphenoxy)-2-methoxybenzoic acid* **(5-73)** (0.18 g, 60%) as pale yellow gum (Found: mol. wt. 410.0768. $C_{19}H_{19}O_8{}^{35}Cl$ requires: mol. wt. 410.0768). ^1H n.m.r. ($CDCl_3$) δ 1.44, 3H, t, *J* 7Hz, CH_2CH_3; 2.50, 3H, s, ArMe; 3.69 and 4.01, each 3H, s, OMe; 4.44, 2H, q, *J* 7Hz, CH_2CH_3; 6.37, 1H, s, H6'; 6.68, 1H, d, *J* 9Hz, H5; 7.40, 1H, d, *J* 9Hz, H4; 11.38, 1H, s, OH.

Ethyl 2-Chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9-oxo-9H-xanthen-7-carboxylate **(5-74)**

The foregoing carboxylic acid **(5-73)** (0.43 g, 1.1 mmol) was dried by azeotropic distillation with toluene and then dissolved in anhydrous toluene (10 ml) and trifluoroacetic anhydride (4 ml). The mixture was stirred at room temperature for 20 h and then diluted with ethyl acetate and washed with aquous sodium carbonate solution, water and brine and then dried ($MgSO_4$). The residue obtained after removal of the solvent was purified by radial chromatography (SiO_2) using 2-30% ethyl acetate / hexane as eluant. The major band afforded *ethyl 2-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9-oxo-9H-xanthen-7-carboxylate* **(5-74)** (50 mg, 12%) which crystallized from the

eluant as yellow crystals, m.p. 220-225° (Found: mol. wt. 392.0663. $C_{19}H_{17}O_7{}^{35}Cl$ requires: mol. wt. 392.0663). ^1H n.m.r. ($CDCl_3$) δ 1.42, 3H, t, *J* 7Hz, CH_2CH_3; 2.40, 3H, s, ArMe; 3.89 and 4.01, each 3H, s, OMe; 4.45, 2H, q, *J* 7Hz, CH_2CH_3; 7.33, 1H, d, *J* 9Hz, H2; 7.76, 1H, d, *J* 9Hz, H3; 12.90, 1H, s, OH. Mass spectrum *m/z* 394 (20.5%), 392 (M, 63.9), 379 (3.2), 377 (10.6), 348 (13.4), 347 (30.2), 346 (22.5), 333 (25.5), 331 (80.2), 67 (100.0).

*2-Chloro-1,8-dihydroxy-5-methoxy-6-methyl-9*H*-xanthen-9-one (4-Dechlorothiomelin, TH1)* **(1-37)**

A solution of ethyl 2-chloro-8-hydroxy-1,5-dimethoxy-6-methyl-9-oxo-9*H*-xanthen-7-carboxylate **(5-74)** (50 mg, 0.13 mmol), potassium hydroxide (0.5 g), dimethyl sulfoxide (20 ml) and water (7 ml) was heated at 140-145° for 2 h in an atmosphere of nitrogen. The cooled mixture was poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ethyl acetate. The organic extract was washed with water and brine, and then dried ($MgSO_4$). The crude acid obtained after removal of the solvent was azeotroped with toluene and then dissolved in anhydrous diglyme (8 ml). Cuprous oxide (30 mg) and 2,2-bipyridyl (0.1 g) were added, the mixture stirred at room temperature for 10 min and then refluxed for 3 h in an atmosphere of nitrogen. The cooled mixture was poured into a mixture of ice and hydrochloric acid and was extracted with ethyl acetate. The organic extract was washed with water and brine, and then dried ($MgSO_4$). The residue obtained after removal of the solvent was purified by preparative t.l.c. (SiO_2) using 25% ethyl acetate / light petroleum as eluant. The major band afforded 2-chloro-1,8-dihydroxy-5-methoxy-6-methyl-9*H*-xanthen-9-one (4-dechlorothiomelin, TH1) **(1-37)** (15 mg, 38%) which crystallized from the eluant as yellow crystals, m.p. 241-243° (lit.[41] m.p. 224-227°) (Found: mol. wt. 306.0295. $C_{15}H_{11}O_5{}^{35}Cl$ requires: mol. wt. 306.0295). ^1H n.m.r.

($CDCl_3$) δ 2.41, 3H, s, ArMe; 3.91, 3H, s, OMe; 6.66, 1H, s, H7; 7.01, 1H, d, *J* 9Hz, H2; 7.70, 1H, d, *J* 9Hz, H3; 11.28 and 12.50, each 1H, s, OH. Mass spectrum *m/z* 308 (10.5%), 306 (M, 35.3), 293 (31.8), 291 (100.0). Standard t.l.c. R_F values: R_F (A) 0.78; R_F (B) 0.76; R_F (C) 0.83; R_F (E) 0.61. Standard h.p.l.c. RI value: 1.14. The synthetic sample was found to be identical (t.l.c., h.p.l.c.) with a minor metabolite of the lichen *Rinodina thiomela.*

*2-Chloro-1,5,8-trimethoxy-6-methyl-9*H*-xanthen-9-one* **(5-76)**

A mixture of 2-chloro-1,8-dihydroxy-5-methoxy-6-methyl-9*H*-xanthen-9-one **(1-37)** (10 mg, 0.033 mmol), dimethyl sulfate (0.05 ml, 0.53 mmol) and potassium carbonate (0.1 g, 0.7 mmol), in anhydrous acetone (15 ml) was refluxed for 4 h. The cooled mixture was poured into a mixture of ice and concentrated hydrochloric acid and was extracted with ethyl acetate. The organic extract was washed with water and brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was purified by preparative t.l.c. (SiO_2) using 25% ethyl acetate / petroleum as eluant. The major band yielded *2-chloro-1,5,8-trimethoxy-6-methyl-9*H*-xanthen-9-one* **(5-76)** (10 mg, 90%) as a pale yellow gum (Found: mol. wt. 334.0607. $C_{17}H_{15}O_5{}^{35}Cl$ requires: mol. wt. 334.0608). ^1H n.m.r. ($CDCl_3$) δ 2.41, 3H, s, ArMe; 3.91, 3.97 and 4.06, each 3H, s, OMe; 6.58, 1H, s, H7; 7.25, 1H, d, *J* 9Hz, H2; 7.64, 1H, d, *J* 9Hz, H3. Mass spectrum *m/z* 336 (0.2%), 334 (M, 0.9), 321 (0.4), 320 (0.3), 319 (1.2), 305 (0.3), 304 (0.4), 57 (100.0).

*2-Chloro-1-hydroxy-5,8-dimethoxy-6-methyl-9*H*-xanthen-9-one (4-Dechloro-8-O-methylthiomelin)* **(5-2)**

A solution of boron trichloride (0.4 mmol) in dichloromethane (0.4 ml) was added to a stirred solution of 2-chloro-1,5,8-trimethoxy-6-methyl-9*H*-xanthen-9-one **(5-76)** (18 mg, 0.054 mmol) in anhydrous dichloromethane (3 ml) at room temperature and the mixture was stirred at this temperature for 5 h. The solvent was then removed and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with water and brine, and then dried ($MgSO_4$). After the removal of the solvent the crude product was purified by preparative t.l.c. (SiO_2) using 25% ethyl acetate / light petroleum as eluant. The major band afforded 2-chloro-1-hydroxy-5,8-dimethoxy-6-methyl-9*H*-xanthen-9-one **(5-2)** (10 mg, 58%) which slowly crystallized from the eluant to form a pale yellow solid, m.p. 35-38° (Found: mol. wt. 320.0450. $C_{16}H_{13}O_5{}^{35}Cl$ requires: mol. wt. 320.0452). ^1H n.m.r. ($CDCl_3$) δ 2.45, 3H, s, ArMe; 3.92 and 4.01, each 3H, s, OMe; 6.63, 1H, s, H7; 6.98, 1H, d, *J* 9Hz, H2; 7.64, 1H, d, *J* 9Hz, H3; 13.72, 1H, s, OH. Mass spectrum *m/z* 322 (0.1%), 320 (M, 0.3), 305 (0.3), 302 (0.2), 284 (0.4), 57 (100.0). Standard t.l.c. R_F values: R_F (A) 0.64; R_F (B) 0.39; R_F (C) 0.51; R_F (E) 0.29. Standard h.p.l.c. RI value: 0.66. The synthetic sample was found to be identical (t.l.c., h.p.l.c.) with a minor metabolite of the lichen *Rinodina thiomela*.

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