SYNTHESIS OF AN ARYL PHOSPHONATE VIA THE ANIONIC PHOSPHO-FRIES REARRANGEMENT

A THESIS PRESENTED IN PARTIAL FULFILLMENT

OF THE REQUIREMENTS FOR THE DEGREE OF

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ABSTRACT

Zearalenone (**1**) is a mycotoxin, which reduces fertility in sheep and leads to substantial production losses in New Zealand. Catalytic antibodies are proposed as a potential approach to reducing the problem. This thesis describes progress toward the synthesis of the aromatic fragment of a transition-state analogue for the hydrolysis of the zearalenone lactone. The key step in the synthesis is an anionic phospho-Fries rearrangement; this relatively novel transformation is reviewed. α-Resorcylic acid (**36**) was converted to three different substrates, each with potential to undergo the O→C transfer of the dimethylphosphoryl moiety. Methyl 3-dimethylphosphato-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]benzoate (**117**) was prepared in three steps and 40% overall yield, but the *tert*-butyldimethylsilyl (TBDMS) protecting group was found to be unstable to phenolate anions. (2-Bromo-3,5-dibenzyloxyphenyl)-1,3-dioxolane (**154**) was prepared but further elaboration required hydrogenolytic cleavage of the benzyl ethers which was incompatible with the Ar-Br linkage. Finally, Ethyl 3-dimethylphosphate-5-(*p*-methoxybenzoxy)benzoate (**167**) was prepared in three steps and 25% overall yield. Treatment with LDA at –78 °C led to the formation of **166**, rather than the desired regioisomer **165**, as a result of lithium preferentially coordinating to the phosphoryl and OPMB groups.

ACKNOWLEDGEMENTS

Firstly, a huge thanks to my supervisor Dr. Carol M. Taylor. Your endless guidance, support and encouragement were very much appreciated. I have gained invaluable knowledge and skills from my time spent with you. I thoroughly enjoyed my project and would never have completed it without you behind me, so thank you!

Thank you also to Dr. Will Barker and Dr. Renaud Hardre who supplied my time in the lab with many laughs, and of course all your help and advice.

Chantelle, your friendship has been invaluable to me this year. Thanks for all the love and support throughout the year. It was great having someone to whinge too when the boys were hassling beyond what I could take, and for all the muffin (or cookie) breaks.

Lastly I would like to thank my family for all their endless love and support. Dad for all the encouragement to continue on with my study. Mum for telling dad when enough was enough! My big sis Sarah, for all your prayers and phone calls, a listening ear when I needed it. Daniel, giving me someone to talk to when I come home, plus all those South Park cartoons you made me watch! I love you all heaps!

TABLE OF CONTENTS

ABBREVIATIONS.

Ar-M	aromatic metal species
BDH	British drug house
BuLi	*n*-butyl lithium
COSY	correlation spectroscopy
°C	degrees Celsius
d	doublet
DDQ	2,3-dichloro-5,6-dicyanoquinone
DEPT	distortionless enhancement by polarization transfer
DIA	N,N-diisopropylamine
DIEA	N,N-diisopropylethylamine
DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
δ	chemical shift
EI	electron impact
equiv.	molar equivalent(s)
FAB	Fast atom bombardment
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
hr(s)	hour(s)

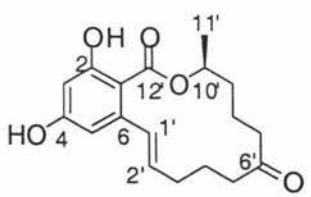
HRMS	high resolution mass spectroscopy
Hz	Hertz
J	coupling constant
LDA	lithium diisopropylamide
$LiAlH_4$	lithium aluminum hydride
LRMS	low resolution mass spectroscopy
m	multiplet
MeCN	acetonitrile
min(s)	minute(s)
mmol	millimole
m.p.	melting point
MS	mass spectrometry
m/z	mass to charge ratio
NBA	Nitrobenzyl alcohol
NBS	*N*-Bromosuccinimide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Pd/C	palladium on carbon
PMB	*p*-methoxybenzyl
ppm	parts per million
p-TSA	para-toluene sulfonic acid
q	quartet
R*f*	Retardance factor
rt	room temperature

§	section
t	triplet
TBAF	tetrabutylammoniumfluoride
TBDMS	*tert*-butyldimethylsilyl
TBDMSCl	*tert*-butyldimethylsilyl chloride
THF	tetrahydrofuran
tlc	thin layer chromatography
UV	ultra violet

1. INTRODUCTION

1.1 Zearalenone: the problem

Zearalenone [6-(10-hydroxy-6-oxo-*trans*-1-undecenyl)-β-resorcylic acid lactone, **1**] is an oestrogenic mycotoxin produced by various *Fusarium* fungal species. The discovery of the mycotoxin followed reports of oestrogenism in swine herds as early as 1927; symptoms were collectively referred to as hyperoestrogensim.[1] McNutt *et al.* attributed the outbreak to feeding on spoiled corn, which was harvested during an unusually wet autumn, and stored over the winter.[2] Reports of hyperoestrogenism in swine continued over the next 20 years throughout the USA and Australia. In 1952, McErlean reported the isolation of *Fusarium graminearum* from mouldy barley feed which had been implicated in a case in Ireland. He hypothesized that the fungus produced a toxin, which was responsible for the symptoms. Stob *et al.* in (1962) were the first to isolate an active substance from the cultures of *Fusarium*,[1] which was characterised by Urry *et al.* in 1966.[3]

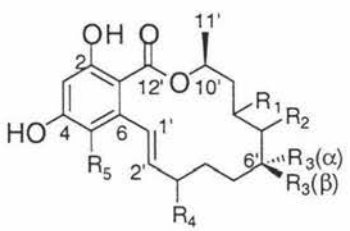


(*S*)-zearalenone (**1**)

Mycotoxins produced by *Fusarium* fungi have been reported worldwide, being found in foodstuffs in the USA, Japan and Europe.[4] The fungus develops in grain during storage

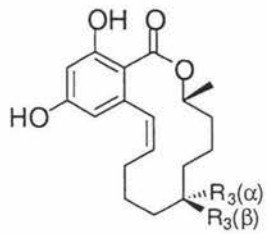
when moisture reaches more than 23%. Decreasing autumn temperatures provide optimal conditions for the biosynthesis of zearalenone.[5] Analysis of the feedstuffs associated with animals showing signs of oestrogenism, usually reveals significant amounts of zearalenone. On occasion, no signs of the mycotoxin were found, leading to the discovery of derivatives of zearalenone.[6] Mirocha *et al.* reported the occurrence of at least seven derivatives of zearalenone from *Fusarium roseum* growing in culture on corn.[5,7] In 1985, they reported six additional oestrogenic compounds, which had not previously been identified from natural sources.[8] These derivatives are summarised in Tables 1.1-1.3.

Table 1.1 *trans*-Zearalenone Derivatives



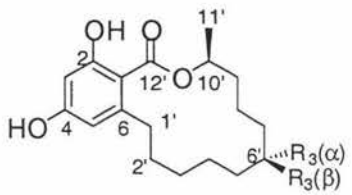
Compound	No	R_1	R_2	R_3	R_4	R_5
zearalenone	**1**	H_2	H_2	O	H_2	H
α-zearalenol	**2**	H_2	H_2	OH(α)	H_2	H
β-zearalenol	**3**	H_2	H_2	OH(β)	H_2	H
8'-hydroxyzearalenone	**4**	OH	H_2	O	H_2	H
6', 8'-dihydroxyzearalene	**5**	OH	H_2	OH	H_2	H
3'-hydroxyzearalenone	**6**	H_2	H_2	O	OH	H
5-formylzearalenone	**7**	H_2	H_2	O	H_2	CHO
7'-dehydrozearalenone	**8**	H	H	O	H_2	H

Table 1.2 *cis*-Zearalenone Derivatives



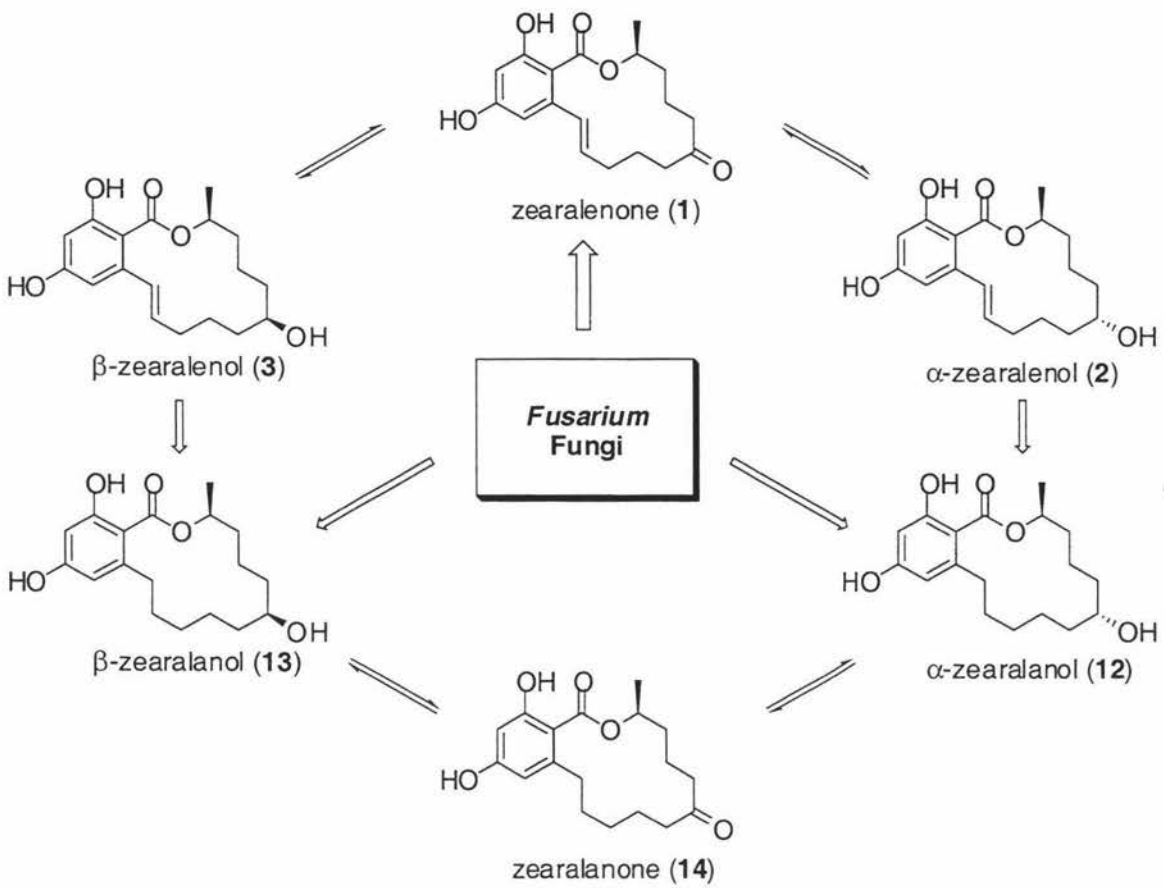
Compound	No	R_3
α-zearalenol	**9**	OH(α)
β-zearalenol	**10**	OH(β)
zearalenone	**11**	O

Table 1.3 Zearalanone Derivatives



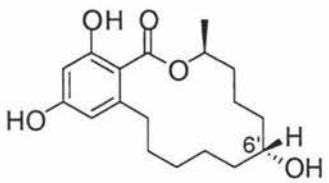
Compound	No	R_3
α-zearalanol	**12**	OH(α)
β-zearalanol	**13**	OH(β)
zearalanone	**14**	O

Zearalenone can be transformed to zearalenols and zearalanols as outlined in Scheme 1.1, by mammalian metabolic pathways.[9] These compounds tend to be more oestrogenic than zearalenone itself and are produced endogenously by some *Fusarium* species.

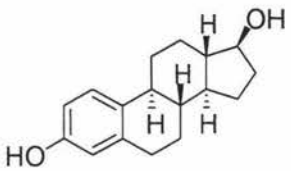


Scheme 1.1: Zearalenone and related metabolites[10]

Zearalenone and its bioactive derivatives produce a true oestrus as well as the more general responses associated with oestrogens. For example, zearalanol has anabolic properties, which have led to its use as a growth promoter for beef cattle. Most of the derivatives have been shown to be more oestrogenic than zearalenone, with *trans*-α-zearalenol (**2**) being three to four times more potent. *In vitro,* zearalanol (**12**) competitively displaces estradiol from oestrogen receptors. A model three-dimensional structure of α-zearalanol (**12**) showed that it has comparable length (10-11 Å) and lipophilicity to that of estradiol (**15**), the ubiquitous steroidal oestrogen.[11] This similarity in overall topology and polarity may explain the affinity for the oestrogen receptor sites.



α-zearalanol (**12**)



17β-estradiol (**15**)

These derivatives likely all contribute to the total oestrogenic effects in mammals to varying extents. Studies on the relative binding affinities of zearalenone derivatives for the oestrogen receptor, measured by a competitive binding assay with 17β-estradiol (**15**), showed the importance of the free 6'-hydroxy group for binding.[12] Reduction of the olefin also enhanced activity.[5]

Although zearalenone is of relatively low toxicity, its role as a mammalian endocrine disrupter is being recognised.[13] Swine appear to be most sensitive to zearalenone, but the compound has also been implicated in the infertility of both cattle and sheep. Most problems derived from the ingestion of the mycotoxin have been traced to contaminated feedstuffs, affecting only housed livestock, fed grain-based feedstocks. This is a major issue for the U.S. swine industry.[14]

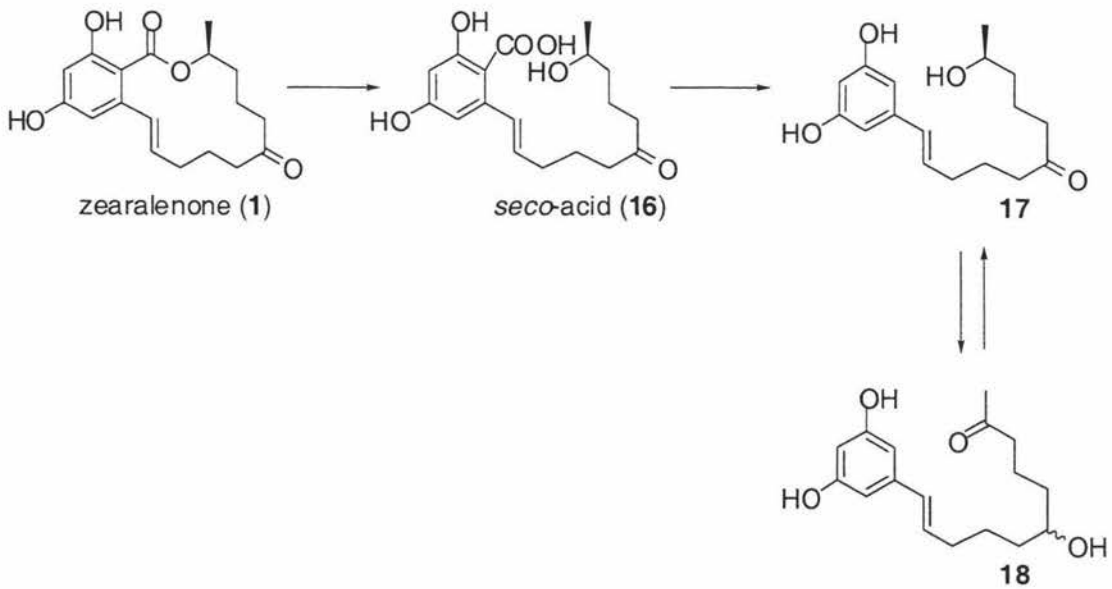
New Zealand livestock are kept outdoors and fed on grass pastures, grazed directly or with hay/silage.[15] Pastures in New Zealand contain several *Fusarium* species capable of producing the mycotoxin, with seven predominant species: *F. acuminatum, F. avenacum, F. crookwellense, F. culmornum, F. gramium, F. oxysporum, F. semitectum.*[10,16] The two most common species, *F. crookwellense* and *F. culmorum,* produce zearalenone at consistently high levels.

As previously stated, optimal fungal growth and concomitant zearalenone production occurs during autumn, which provides favourable grass temperature, humidity and day length. During the mating period, peak levels of the oestrogenic mycotoxin in pastures will often be sufficient to reduce a ewe's fertility. Studies show that over 30% of New Zealand sheep flocks have sufficient exposure to the mycotoxin to reduce ovulation.[14] The decline in ovulation rate in sheep is proportional to the dose of zearalenone.[17] Lower doses result in a reduction in numbers of ewes with multiple ovulations, while higher doses result in a proportion of ewes becoming anovulatory. The failure of ewes to ovulate is most probably due to an interference with LH (lutenizing hormone) released from the pituitary. While cattle also graze on affected pastures, they are mated in spring when the toxin levels are lower.[18]

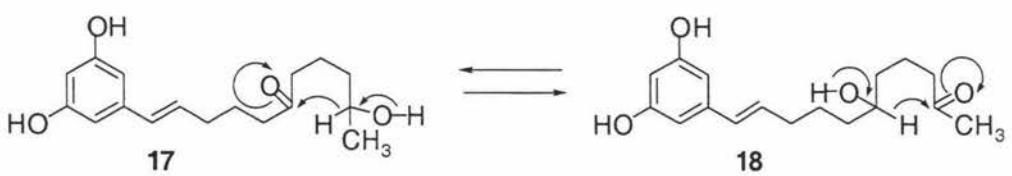
Lambing production losses attributed to this mycotoxin, make zearalenone one of the country's largest animal health problems. Current research is focusing on the development of management strategies based on the use of crops or pastures that do not support *Fusarium* growth and zearalenone production. Kramer *et al.* demonstrated chicory as an effective feed; reduced levels of zearalenone were observed prior to mating.[19]

Other approaches have also been investigated to eliminate the mycotoxin and its effects. Screening of 150 fungal species identified one microbe, *Gliocladium roseum,* which is capable of transforming zearalenone into compounds **17** and **18** in 80-90% yields. This presumably occurs via cleavage of the lactone by an esterase, giving the unstable *seco*-acid (**16**) that undergoes spontaneous decarboxylation (Scheme 1.2).[12] Compound **17** can rearrange to give compound **18**. An internal hydride shift was proposed, proceding via a 6-

membered transition state, to account for the formation of **18** (Scheme 1.3). These compounds showed no inhibition of the oestrogen receptor.



Scheme 1.2: Metabolism of zeraralenone by *Gliocladium roseum*



Scheme 1.3: Proposed isomerisation mechanism

The total biodegradation of zearalenone by a bacterial culture was demonstrated by Megharaj *et al.*[20] However, they were unable to show whether the degradation was achieved by a single species of bacteria, or if it required the presence of several.

A vaccine, Androvax®, has been developed to generate antibodies that render a change in the hormone balance within the ewe, increasing its ovulation rate.[21] While this counteracts the detrimental effects of zearalenone, it is not a direct approach.

1.2 Catalytic antibodies: the concept and potential utility

The first successful examples of catalytic antibodies were reported in 1986, demonstrating the catalysis of the hydrolysis of esters and carbonates.[22] The concept utilises the immune system's extraordinary ability to generate antibodies *in vitro*, in vast quantities.[23] Antibodies have high affinity and specificity toward their antigens, and can be generated in response to almost any molecule. Reactions are catalysed by antibodies, which selectively bind high-energy transition states along the reaction pathway. This enzyme-like behaviour results in lowered activation energy for the reaction, and thus catalysis.

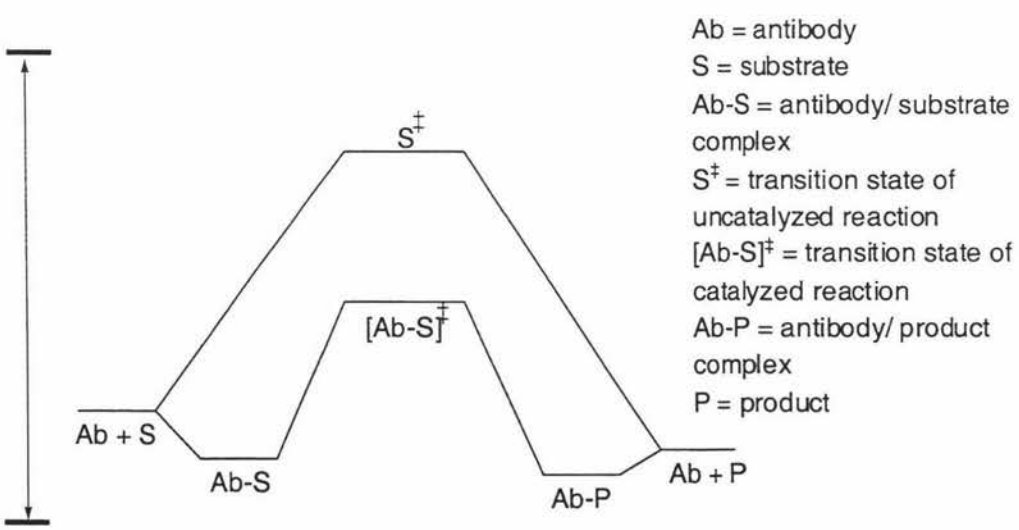


Figure 1.1. Energy profile for antibody catalysed reaction[24]

Antibodies are large proteins consisting of constant regions as well as variable regions (Figure 1.2). The latter are responsible for the binding of antigens. The constant region contains heavy and light chains, plus a hinge region held together by a series of disulfide bonds.

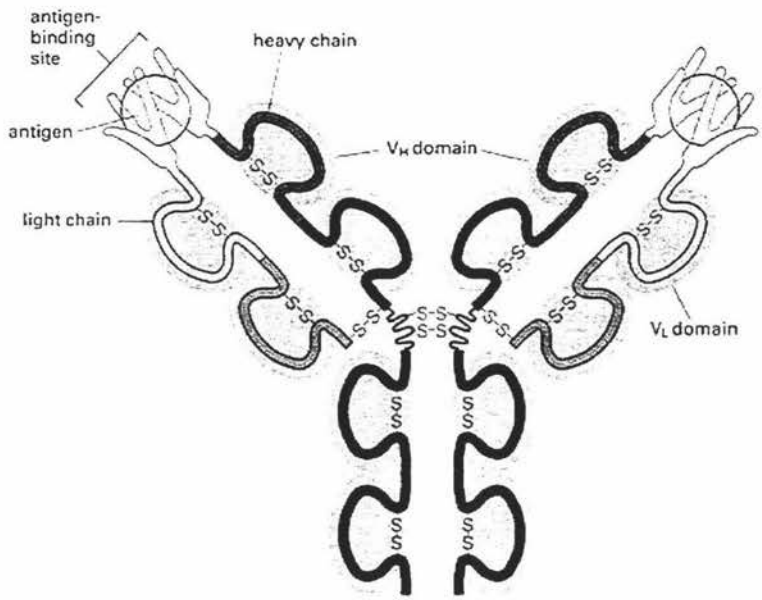
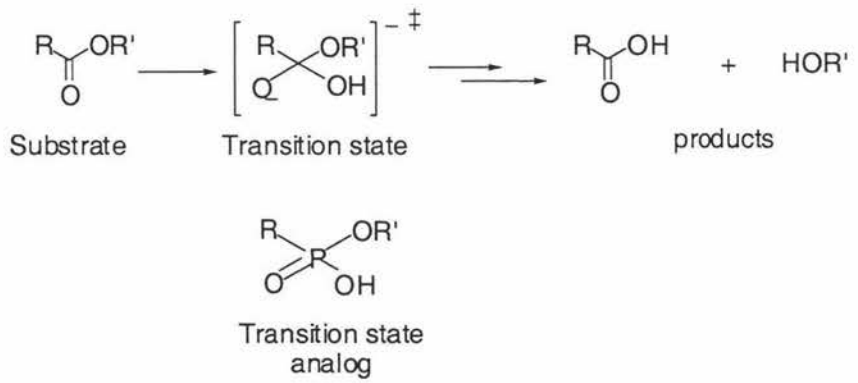


Figure 1.2. Morphology of an antibody[25]

The generation of antibodies which successfully catalyse a reaction, requires the design of an appropriate transition state analogue, called a hapten. The hapten is used to generate antibodies that are complementary and therefore ought to selectively bind the rate-determining transition state, reducing the entropy requirements of the desired transformation.

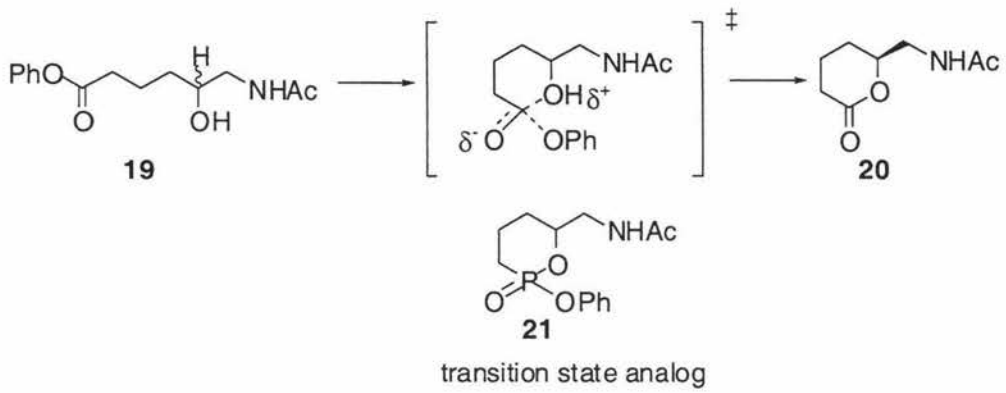
One example of the use of this concept is the catalysed carboxylate ester hydrolysis demonstrated by Lerner (Scheme 1.4).[21] The rate determining step of the ester hydrolysis

involves the formation of a negatively charged tetrahedral transition state. They used a stable phosphonate transition state analogue to mimic both the tetrahedral geometry and charged nature. The antibody catalysed reaction showed an acceleration of 10^3-10^4 compared to background hydrolysis.



Scheme 1.4: Antibody-catalysed ester hydrolysis

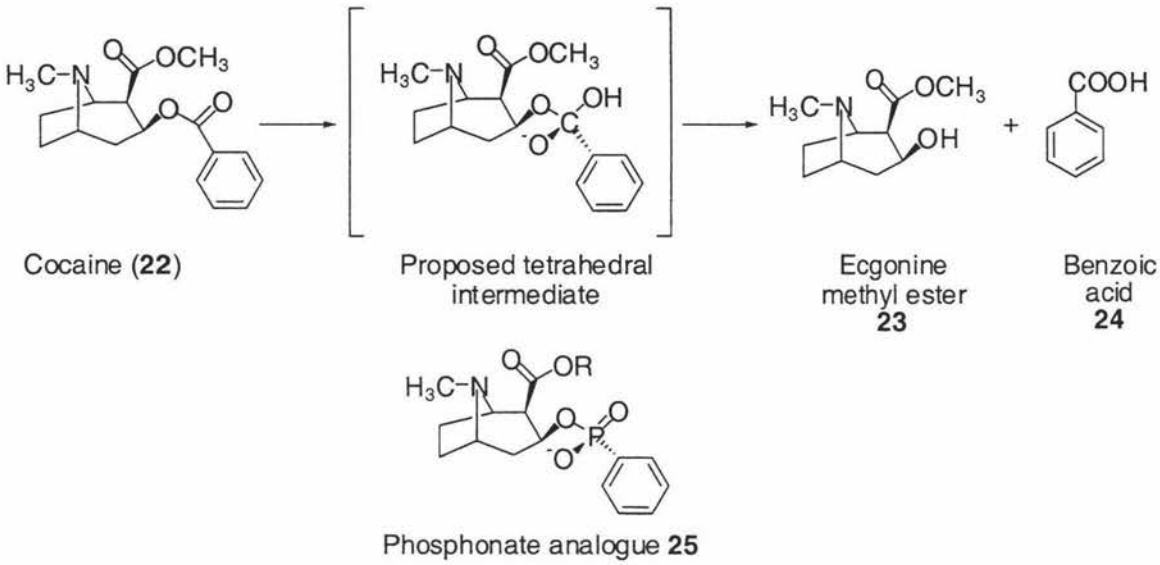
Napper *et al.* used catalytic antibodies to facilitate a stereospecific lactonization (Scheme 1.5). This tested the antibody's enzyme-like ability to not only reduce the entropy requirements, but to choose between two reaction pathways (*i.e.*, discriminate between two diastereoisomeric transition states).[26] The transition state was again mimicked by a phosphonate ester.



Scheme 1.5: Antibody-catalysed lactonization

The cyclization gave one enantiomer of the lactone **20** in 94 percent enantiomeric excess, demonstrating the potential use of catalytic antibodies for chemical transformations that require stereochemical control. This example is mechanistically relevant to the current proposal, although it is the reverse transformation and a smaller lactone ring.

The potential of catalytic antibodies to destroy toxins *in vivo* has already been recognised, with antibodies to treat cocaine addiction.[27] Cocaine abuse is a major public health problem in the United States.[28] Cocaine's exceptional reinforcing effect renders it resistant to treatment. Catalytic antibodies offer an alternative to the therapeutic approaches based on the pharmacology of the cocaine receptor. Hydrolysis of cocaine's benzoyl ester yields fragments that contain none of cocaine's stimulant or reinforcing activities (Scheme 1.6). Landry *et al.* used the phosphonate monoester **25** as a stable analogue of the tetrahedral intermediate of the ester hydrolysis.[27a]

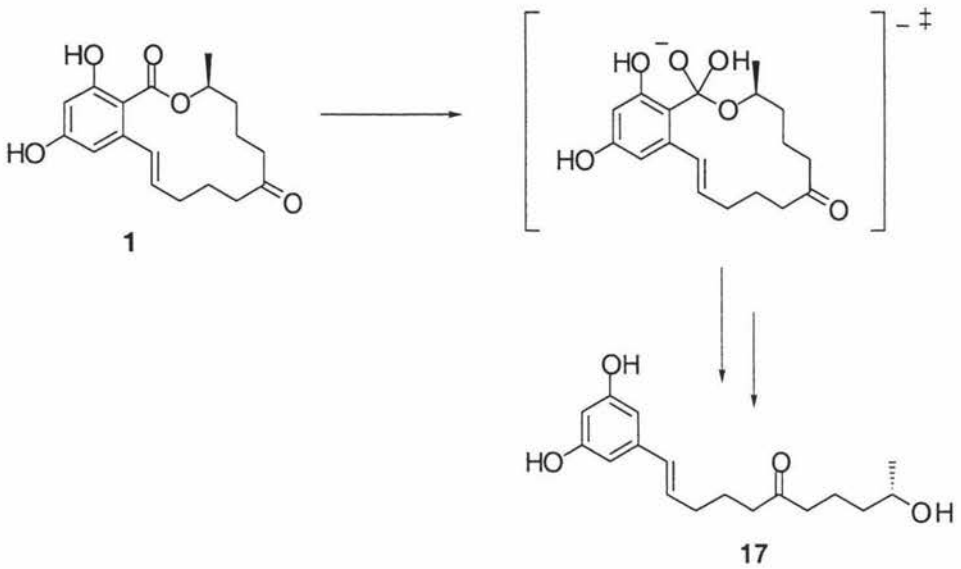


Scheme 1.6: Antibody-catalysed cocaine hydrolysis

The use of catalytic antibodies to catalyse the hydrolysis of organophosphorous nerve agents is also being developed for the immunisation of soldiers by the US army.[29]

1.3 Hydrolysis of the zearalenone lactone

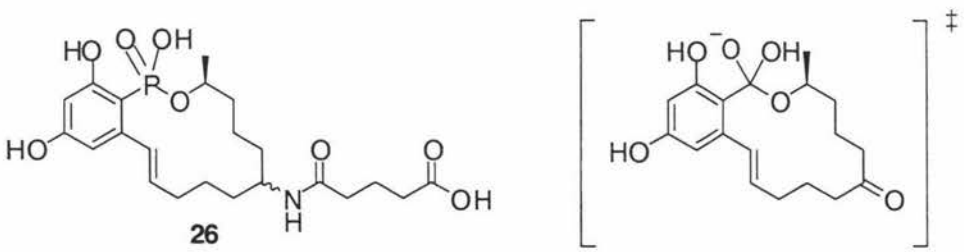
As mentioned previously, hydrolysis of the 14-membered lactone ring of zearalenone leads to a *seco*-acid, which undergoes further spontaneous degradation to non-oestrogenic products (Scheme 1.7). If this degradation could be triggered *in vivo* by catalytic antibodies, it could dispel the oestrogenic effects of the mycotoxin. The hydrolysis of the lactone ring leads to a negatively charged tetrahedral transition state, presumably resulting from nucleophilic attack by a water molecule on the acyl centre.



Scheme 1.7: Breakdown of zearalenone to non-oestrogenic compounds

1.4 Hapten design

Our proposed hapten (**26**) is a stable transition state analogue for the hydrolysis of zearalenone.

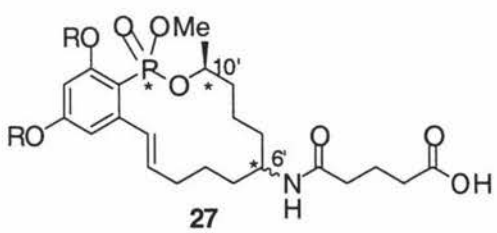


It contains a phosphonomacrolactone. Phosphonate esters have been used extensively in the design of haptens for the generation of catalytic antibodies possessing esterase activity as discussed earlier. The slightly longer phosphorus-oxygen bonds mimic the partially broken/formed bonds in the transition state. The tetrahedral geometry of the phosphonate

ester also mimics the charged tetrahedral transition state. The third feature is the succinimidal linker chain attached at C6'. This will ultimately be used to conjugate the hapten to a carrier protein, to allow recognition by the immune system. Sensitive ELISA assays for zearalenone have already been developed by our collaborators at AgResearch, which permits the rapid analysis of large numbers of pasture, blood and urine samples for the presence of zearalanone, α- and β-zearalenol.[15] Overnight incubation with β-glucuronidase hydrolyses zearalenol-glucuronide conjugates. Antibodies generated from zearalenone conjugated to a carrier protein, recognise the ground state zearalenone molecule and related derivatives. This interaction is utilised to quantify zearalenone samples via a colour reaction that can be read by spectrophotometers.

The development of the ELISA assay (*vide infra*) at AgReasearch, involved the conjugation of zearalenone to a carrier protein via C6'. From this work, we know that attachment of the linker chain at this position does not affect the viability of antibodies derived therefrom.

In the synthesis of hapten **26** an advanced intermediate such as **27** will have three stereogenic centres, compared to one at C10' in zearalenone. From a synthetic perspective, it is desirable and more aesthetically pleasing to work with a single stereoisomer. These stereocentres warrant some discussion.



27

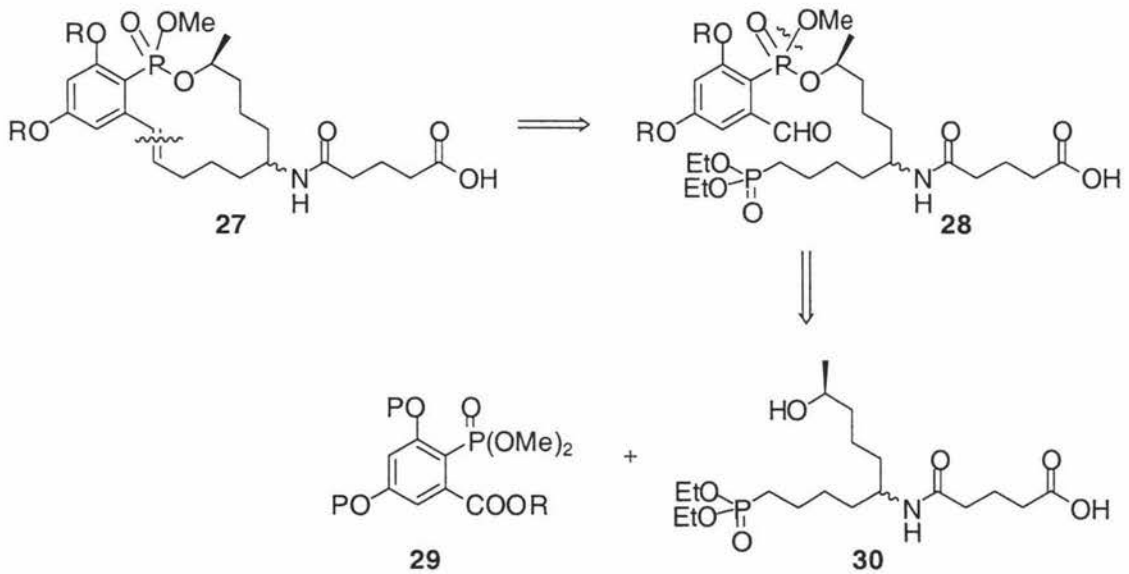
1) The phosphate group introduces one of the new stereocentres to compound **27**. There is little information on the stereoselective formation of such esters. Prior to immunisation, the phosphate ester is hydrolysed to give the phosphonic acid, thus relinquishing its stereogenicity. Hence, it is probably acceptable to work with a mixture of diastereoisomers arising at P.
2) Ideally, our synthesis should emulate the naturally occurring configuration at C10' of zearalenone, even though the presence of the phosphonate will significantly alter the geometry in this region of the molecule.
3) The third stereocentre occurs at C6'. As previously mentioned, the configuration at this centre should not be of any consequence. However, working with a single isomer is easier and as there is considerable methodology available for stereoselective reductive animation, we might as well take advantage of this.

Once the hapten has been synthesised it will be passed on to our collaborators at AgResearch. Here it will be conjugated to a carrier molecule and used to generate antibodies. Antibodies with a strong affinity for the hapten should facilitate the hydrolysis of the lactone by selectively binding the transition state and thus serving as a catalyst.

1.5 Retrosynthetic analysis of the hapten

Retrosynthetic analysis of our hapten suggests two major disconnections to give an aromatic and an aliphatic fragment, compounds **29** and **30** respectively. The synthetic

challenge is thereby reduced to two subtargets. Union of the two fragments ought to yield the macrocyclic structure.

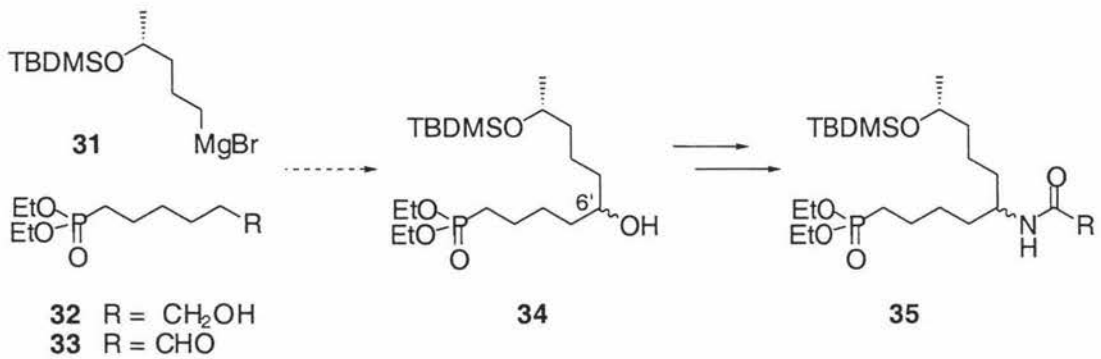


Scheme 1.8: Retrosynthetic analysis of the proposed hapten

The synthesis of our hapten will take advantage of the tremendous body of chemistry developed in previous syntheses of zearalenone. The introduction of the phosphonolactone, however provides new synthetic challenges. Throughout this synthesis, we intend to utilise organophosphorus chemistry, including such reactions as the anionic phospho-Fries rearrangement, the Mitsunobu reaction for phosphonate ester formation, and the Horner-Emmons reaction.

The aliphatic fragment will be assembled from three sub-fragments. A Grignard reaction between compounds **31** and **33** is proposed, which should give rise to compound **34**. The secondary alcohol in compound **34** provides a "handle" at C6' for the attachment of the

linker. Samuel Brodie in our group has prepared a racemic mixture of compound **31**, as well as synthesising compound **32**.



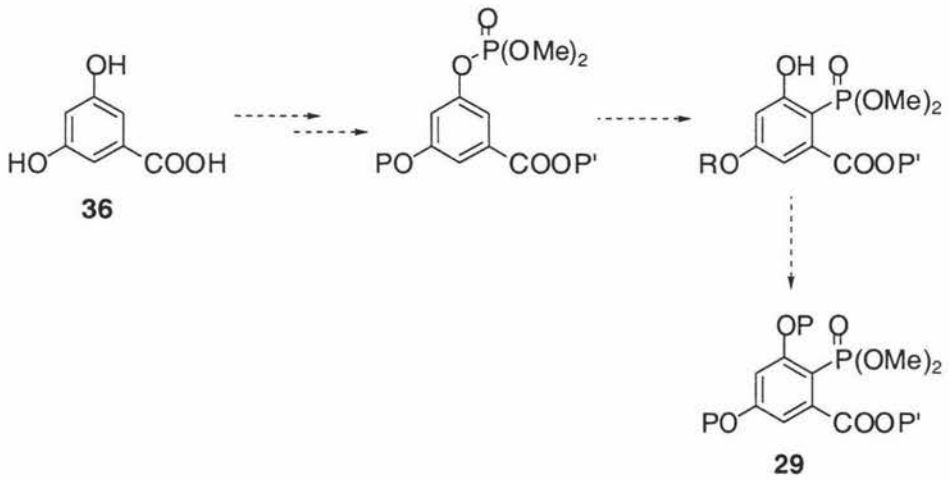
Scheme 1.9: Assembly of aliphatic fragment

For this synthesis to be economically viable on an industrial scale, inexpensive starting materials and reagents must be used. The aromatic fragment will be synthesised from α-resorcylic acid, which is commercially available at a low cost.

Scheme 1.10: Retrosynthetic analysis of aromatic fragment

In a forward sense, the synthesis of the aromatic fragment is outlined in Scheme 1.11. The acid functionality will firstly be protected as an alkyl ester. Protection of one of the two equivalent phenol groups, followed by phosphorylation of the remaining free phenol leads into the key step. To produce the desired phosphonate, the anionic phospho-Fries

rearrangement will be invoked. This novel transformation is the cornerstone of our synthesis and is discussed in detail in Chapter 2. Protection of the ensuing phenol gives the desired protected aromatic fragment.



Scheme 1.11: Proposed synthesis of aromatic fragment

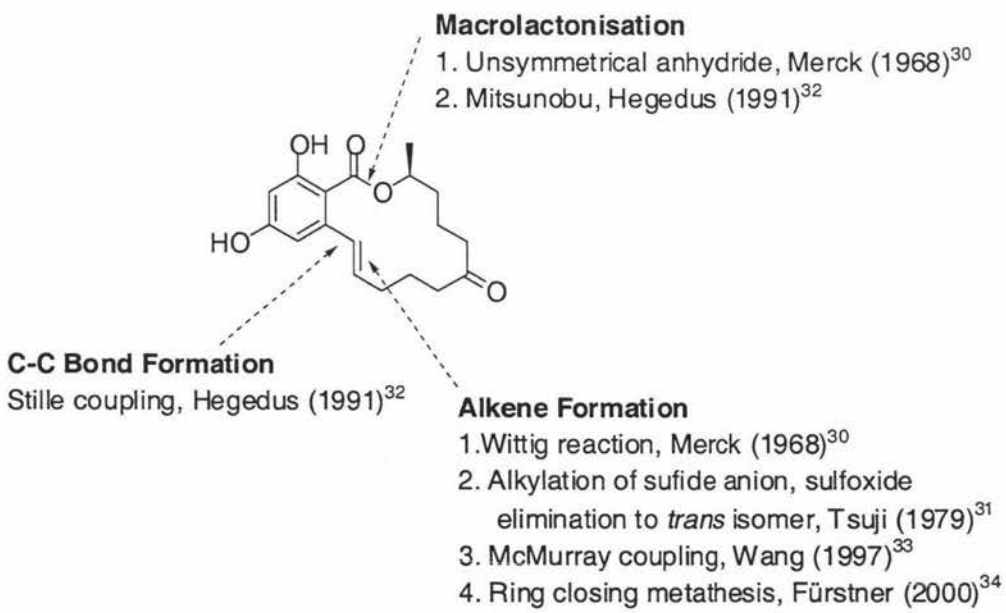
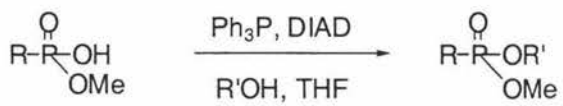


Figure 1.3. Summary of methods used to form key linkages in syntheses of zearalenone

In 1991 Hegedus *et al.* published the first enantiospecific synthesis of (*S*)-(-)-zearalenone. The fragments were linked by a stereospecific Mitsunobu esterification, which proceeds with inversion of the stereochemistry at the alcohol carbon. Palladium-catalysed Stille coupling gave the desired *trans* double bond in the macrocyclization. Most subsequent syntheses have employed the Mitsunobu reaction for ester formation, but vary considerably in the cyclization step.

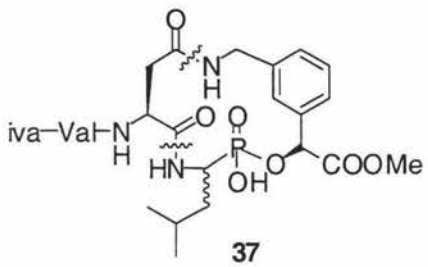
The Mitsunobu reaction has been extended to the preparation of phosphonate esters.[35] The reaction was first reported by Campbell in 1992 and is a mild and effective method utilizing the redox chemistry of triphenylphosphine and diisopropyl azodicarbonate (DIAD) to condense an acidic reagent with primary or secondary alcohols.[36]



Scheme 1.12

The synthesis of macrocyclic phosphonates presents a challenge to the synthetic chemist. There is only one known example of phosphonate ester formation as the ring forming step.

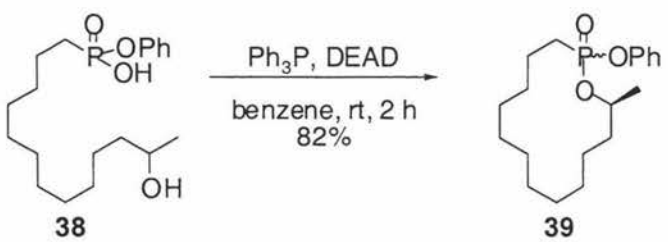
Smith and Bartlett reported the synthesis of macrophosphonolactones as inhibitors of penicillopepsin.[37] They intentionally established the phosphate ester early in the synthesis, due to the difficulty in the formation of such esters. They chose two peptide bonds as potential cyclization sites, indicated by the two disconnections below.



37

Figure 1.4

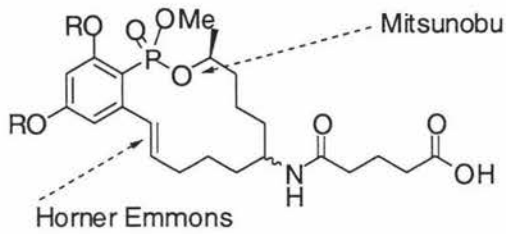
Pungente and Weiler reported the synthesis of a 14-membered cyclic phosphonate using the Mitsunobu reaction for the cyclization step.[38] The reaction gave a 5:1 ratio of two isomers. This was accounted for by fewer steric interactions in the transition state for the ring closure leading to the favoured product.



38 39

Scheme 1.13

Our plan is to join the aromatic and aliphatic fragments of our hapten **27** by phosphonate esterification using the Mitsunobu reaction. Macrocyclization will then be attempted via a Horner-Emmons reaction to form the *trans* double bond.



27

This thesis describes the efforts towards the synthesis of the aromatic fragment (**29**) with the use of the anionic phospho-Fries rearrangement for the key phosphate to phosphonate step.

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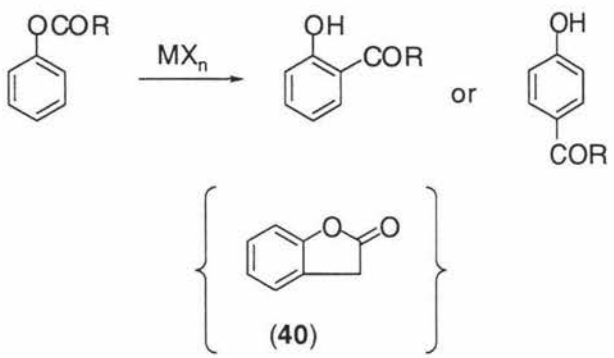
Glossary:

1) Hapten: A small molecule having at least one of the determinant groups of an antigen, that can combine with an antibody but which is not immunogenic unless it acts in conjunction with a carrier molecule.
2) Mycotoxin: Toxin produced by fungal species.
3) Oestrogens: female hormone that controls reproductive cycle
4) Anabolism: metabolic process in which body tissues are synthesised from food.
5) Endocrine: relating to the glands that secrete hormones directly into the bloodstream.
6) Silage: fodder crop harvested while green and partially fermented in a silo.
7) Anovulatory: No longer ovulating.
8) Lutenising Hormone:stimulates ovulation.
9) Pituitary: gland at the base of the brain that helps control growth.
10) Esterase: Enzyme that hydrolyses an ester.
11) Biodegradation: decomposition by natural means.
12) Vaccine: substance designed to cause a mild form of disease to make a person immune to the disease itself.
13) ELISA: Enzyme Linked Immunosorbent Assay.

2. THE ANIONIC PHOSPHO-FRIES REARRANGEMENT

2.1 The Reaction

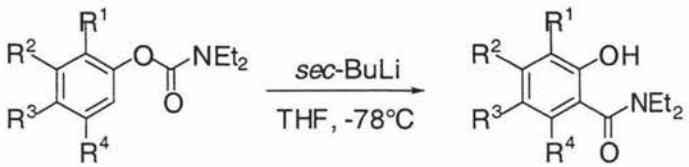
In 1908, while working on derivatives of cumaranone (**40**), Fries and Finck encountered the Lewis acid catalysed rearrangement of aryl esters, to give the corresponding *ortho* or *para*-hydroxyketones (Scheme 2.1).[1]



Scheme 2.1

The rearrangement occurs more readily when the R group is aliphatic (*c.f.*, aromatic). *Ortho* or *para* rearrangement depends on steric and temperature factors, as well as the nature of the metal halide catalyst.

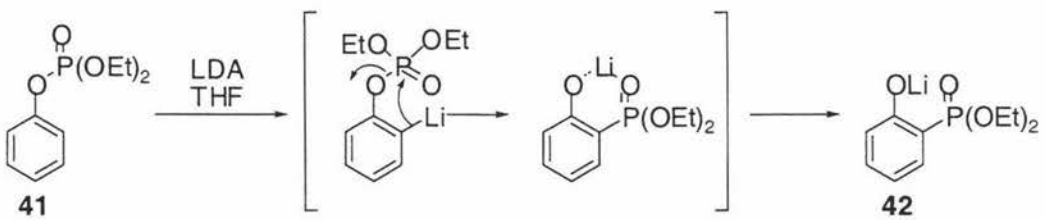
An anionic equivalent of the Fries rearrangement of *O*-aryl carbamates was reported by Sibi and Snieckus.[2] This previously unseen O→C 1,3-carbamoyl migration of the *ortho* lithiated species, enabled the use of the carbamate as a "carrier" of the tertiary amide.



R^1	R^2	R^3	R^4	Yield (%)
H	H	H	H	75
H	H	OMe	H	60
OMe	H	H	H	68
H	H	Cl	H	65

Scheme 2.2

The anionic phospho-Fries rearrangement is an extension of the Fries rearrangement above, which involves a based-induced migration of an arylphosphate to phosphonate (Scheme 2.3).

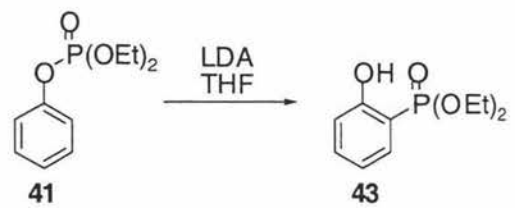


Scheme 2.3

The rearrangement requires deprotonation of the aromatic ring by a strong base to generate the dipole stabilised carbanion.[3] The formation of the strong Li-O bond over the C-Li bond drives the reaction, outweighing the energy loss in the P-O to P-C rearrangement. Due to the *ortho* directing ability of the phosphate group, only the corresponding *ortho* products are seen.

2.2 Early Studies

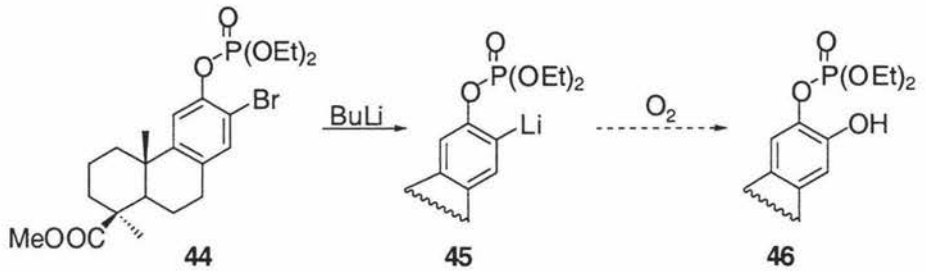
The first anionic phospho-Fries rearrangement was reported by Melvin in 1981.[4] He proposed that *ortho*-metalation by LDA was followed by intramolecular collapse of the intermediate to give an aryl phosphonate (Scheme 2.3). He reported the rearrangement of several diethylphosphates bearing either alkyl or alkoxy substituents on the aromatic ring, with yields ranging from 78-95%. A simple example, discussed on the previous page, is reiterated below.



41 43

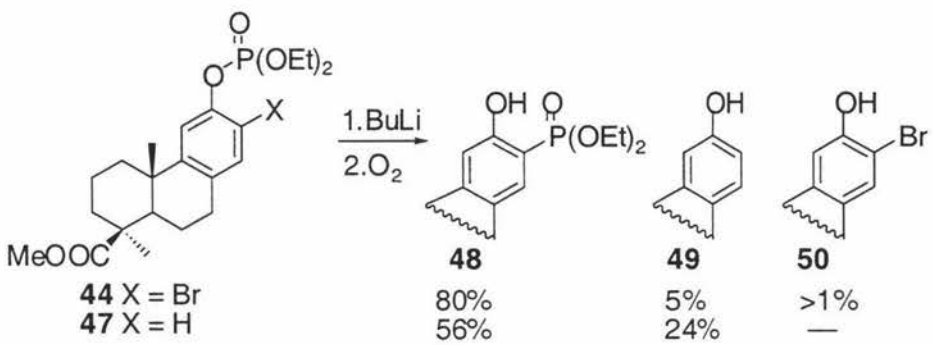
Scheme 2.4

About the same time, Cambie and Palmer inadvertently discovered the reaction while trying to introduce a hydroxy group *ortho* to a phosphate on a podocarpic acid derivative.[5] They proposed that compound **44** on treatment with *n*-BuLi, would undergo halogen-metal exchange. They hoped to trap the aromatic-metal species with molecular oxygen, thereby introducing a hydroxy group *ortho* to the phosphate (Scheme 2.5).



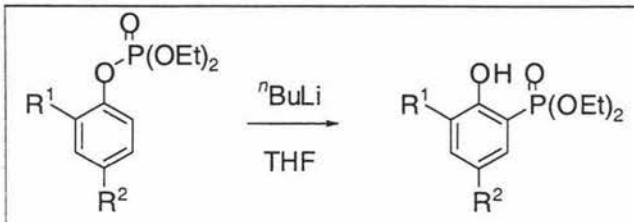
Scheme 2.5

Instead, the reaction yielded the rearranged phosphonate **48** in 80% yield, along with two by-products: methyl 12-hydroxypodocarpa-8,11,13-trien-19-oate (**49**) and the *ortho*-bromo phenol **50**, presumably arising from competing intermolecular nucleophilic attack of the *n*-butyl anion at phosphorus.



Scheme 2.6

The phenolic proton in compound **48** gave rise to a signal at δ 9.77 in the ^{1}H NMR spectrum, indicating intramolecular H-bonding. The large P-C coupling constant (182 Hz) implies a direct C-P bond. In the absence of an *ortho*-bromo substituent, the rearrangement of **47** yielded 56% of the rearranged product and 24% of the phenol. Several rearrangements of simple aryl phosphates were reported, as summarized in Scheme 2.7.

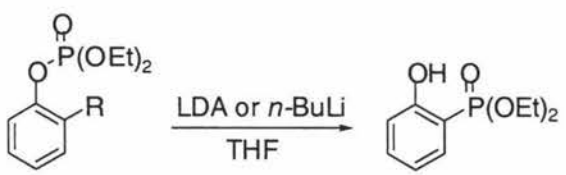


R^1	R^2	Yield
H	H	84%
H	Cl	77%
H	Me	84%
Me	H	92%

Scheme 2.7

2.3 Generating the Ar-M species

A range of different bases has been used, including *n*-BuLi, *s*-BuLi and LDA, to generate the anion in the rearrangement, either by direct metalation or by metal-halogen exchange. The product distribution illustrated in Scheme 2.6 indicates that the rate of formation of the aryllithium species by direct metalation is slower than that by metal-halogen exchange, thus allowing competing nucleophilic attack of *n*-BuLi at the phosphoryl group. Cambie's work also demonstrated the rearrangement of simple phosphates with *n*-BuLi invoking halogen-metal exchange, and compared it to direct metalation. An example is given in Scheme 2.8. He showed that the two methods are equally effective, but the halogen-metal exchange reaction was significantly faster.



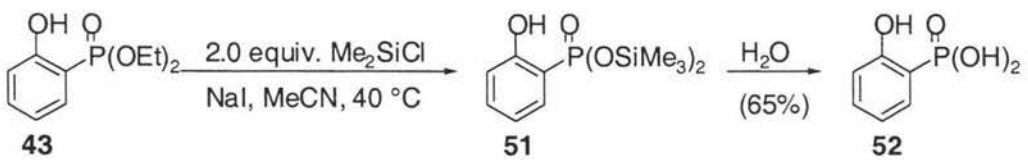
R	Time	Yield(%)
H	1.5 h	90
Br	5 min	95

Scheme 2.8

Heinicke and coworkers investigated the generation of Ar-M species using metallic sodium and magnesium, in the latter case leading to a Grignard reagent.[6] These species participated in the rearrangements, although yields were typically not as good as when Ar-Li intermediates were involved.

2.4 Substituents at phosphorus

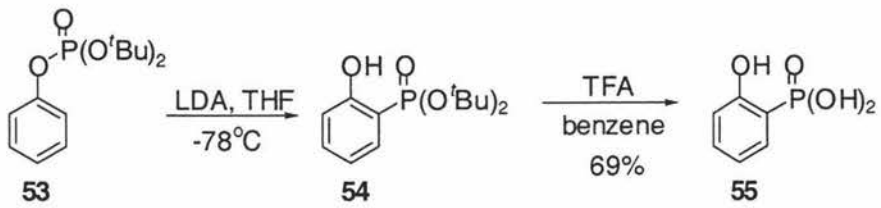
Initial studies used ethyl esters as phosphonic acid protecting groups during the rearrangement. Hydrolysis of the ethyl esters to the corresponding acids required harsh conditions not compatible with acid sensitive functionalities. Trimethylsilyl halides were also employed to remove the esters (Scheme 2.9). Although these conditions were milder, the products were difficult to purify.[7]



43 **51** **52**

Scheme 2.9

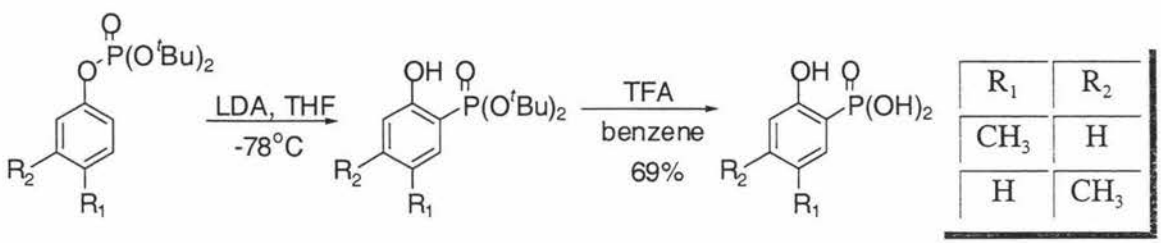
Dwahan and Redmore introduced the use of *tert*-butyl esters instead of the ethyl groups, as deprotection and purification were easier.[8]



53 54 55

Scheme 2.10

They published another paper further investigating the use of di-*t*-butyl esters and their additional advantages.[9] Unlike the ethyl esters, the *t*-butyl esters had the advantage of being solids and so could be purified by crystallisation. As before, deprotection to give the phosphonic acids was also easier.



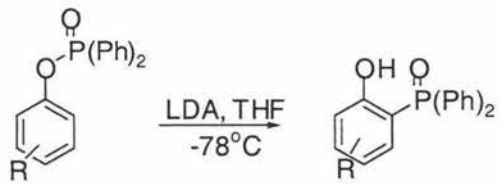
R_1	R_2
CH_3	H
H	CH_3

Scheme 2.11

Casteel commented that rearrangement of substrates incorporating *t*-butyl phosphate esters tended to result in lower yields.[10] She proposed that this was a result of steric hindrance, which could usually be counteracted by the use of halogen-metal exchange.

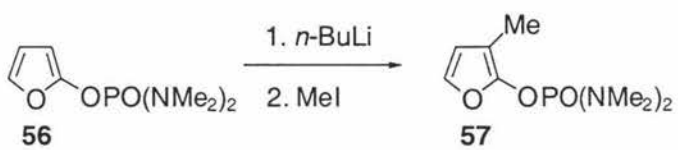
Several substituents other than the dialkoxyphosphoryl groups have been used in the rearrangement.

Diphenylphosphinate groups were used to prepare 2-(diphenylphosphinyl)phenols, via the rearrangement, which are used in the preparation of ligands that can extract ammonium compounds from aqueous to organic phases.[11]



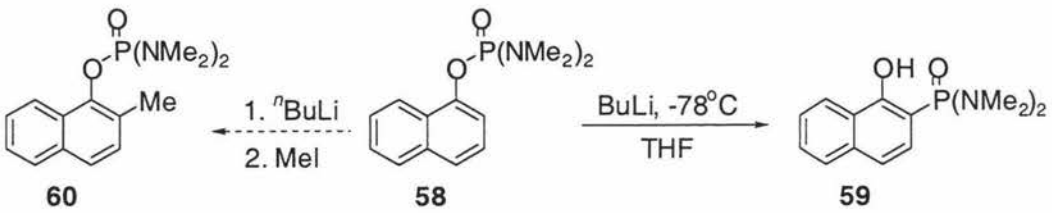
Scheme 2.12

Nasman and Kopola had previously reported the new β-directing substituent *N*,*N*,*N*',*N*'-tetramethyldiamido phosphate (PON) for regioselective lithiation in the 3-position of the furan moiety.[12]



Scheme 2.13

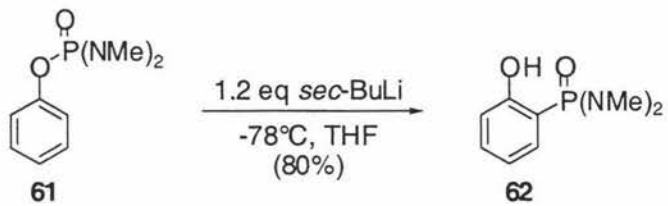
While trying to establish the *ortho*-directing ability of the PON substituent in alkylations, Nasman and Kopola also encountered the rearrangement.[13] Their results showed that the PON group did have good *ortho* activation properties, but due to the rearrangement occurring the desired methylation product **60** could not be obtained.



60 58 59

Scheme 2.14

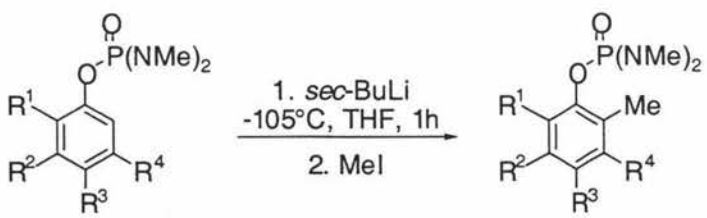
Watanabe *et al.*, also using tetramethylphosphorodiamidates for the *ortho*-lithiation of phenols, saw the same rearrangement of the PON group (Scheme 2.15).[14]



61 62

Scheme 2.15

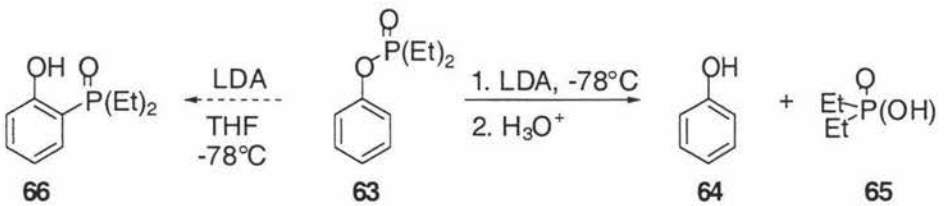
They did however manage to find conditions (*i.e.*. lower temperature) that suppressed the rearrangement and permitted successful *ortho*-methylation of the aromatic ring in high yields (Scheme 2.16).



R^1	R^2	R^3	R^4	Yield (%)
H	H	H	H	87
OMe	H	H	H	87
H	H	H	OMe	75
H	H	OMe	H	91
H	OMe	H	OMe	93

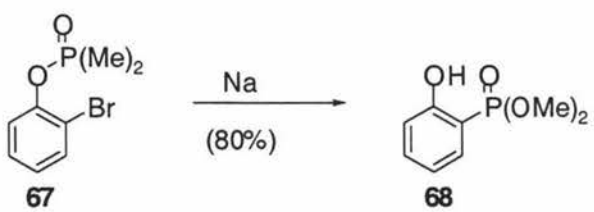
Scheme 2.16

Li and Wang wanted to synthesis a series of phosphinates.[15] They hoped that a similar rearrangement of aryl dialkylphosphinates would occur if treated with LDA at low temperature. Unfortunately, the reaction was unsuccessful, yielding only phenol and dialkylphosphinic acids, presumably resulting from nucleophilic substitution reaction.



Scheme 2.17

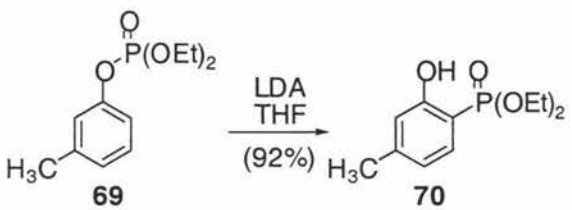
Heinicke *et al.* did manage to achieve rearrangement of dimethylphosphinates via metal-halogen exchange.[16]



Scheme 2.18

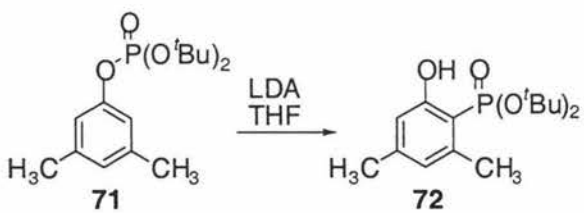
2.5 Effects of existing substituents on the aromatic ring

The initial studies by Melvin, with alkyl and alkyloxysubstituents on the aromatic ring demonstrated some issues regarding regioselectivity of the rearrangement. The regioselectivity observed in Scheme 2.19 is presumably due to the greater steric hindrance of one of the two *ortho* aromatic protons, with migration to the less hindered position occurring.



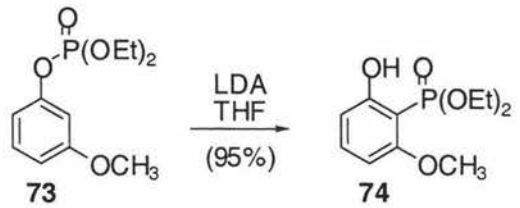
Scheme 2.19

Rearrangement of di-*t*-butyl(3,5-dimethylphenyl)phosphate (**71**) occurred with a 73% yield, confirming that *ortho*-deprotonation still occurred despite the increase in steric hindrance.



Scheme 2.20

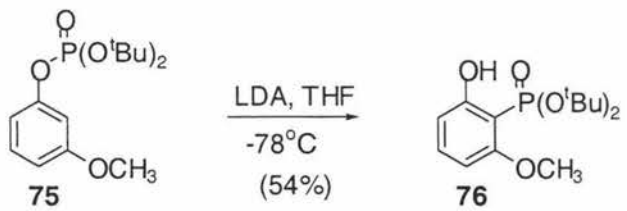
Compound **73** rearranged to the compound **74**, with chelation of the methoxy group directing the rearrangement (Scheme 2.21).



73 74

Scheme 2.21

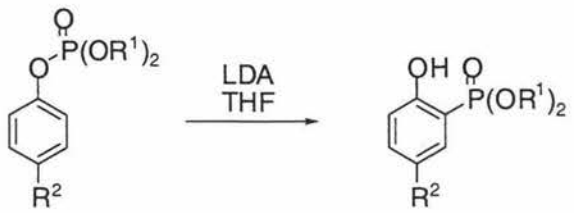
Dwahan and Redmore demonstrated a similar regioselective rearrangement.[17] The rearrangement of di-*t*-butyl (3-methoxyphenyl)-phosphate (**75**) was a highly regioselective migration, with the two *ortho* directing groups working together, to direct the metalation to the 'internal' *ortho* position (Scheme 2.22). The difference in yields for the reactions in Schemes 2.21 and 2.22 could be attributed to the increase in steric bulk due to the *tert*-butyl ester.



75 76

Scheme 2.22

In the same year, Casteel published a paper investigating the electronic and steric effects of substituents on the aromatic ring, showing that both are important in the rearrangement.[18] These results are summarized in Scheme 2.23.

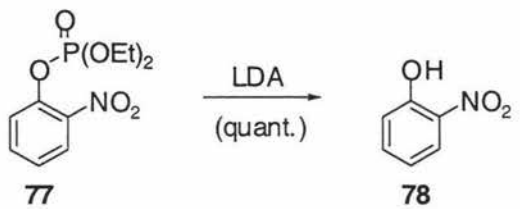


R^1	R^2	Time	Yield (%)
Et	H	1.5 h	90
Et	COO^tBu	4 h	40
^tBu	H	3 h	87
^tBu	COO^tBu	-	0

Scheme 2.23

The presence of *para* electron withdrawing groups (*i.e.,* electronic deactivation), combined with the bulky *tert*-butyl esters, resulted in the rearrangement being completely suppressed in the case of the last example. Comparison of entries 1 and 2, illustrate that the electron-withdrawing *t*-butyl ester slows down the rearrangement considerably.

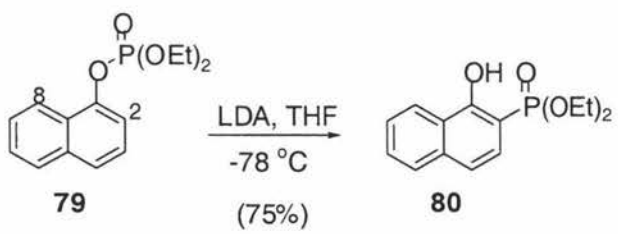
Li and Wang found that electron donating groups facilitate the reaction, but electron-withdrawing substituents promote the nucleophilic attack of the diisopropylamide anion at phosphorus, leading to liberation of the phenol (Scheme 2.24).[15]



Scheme 2.24

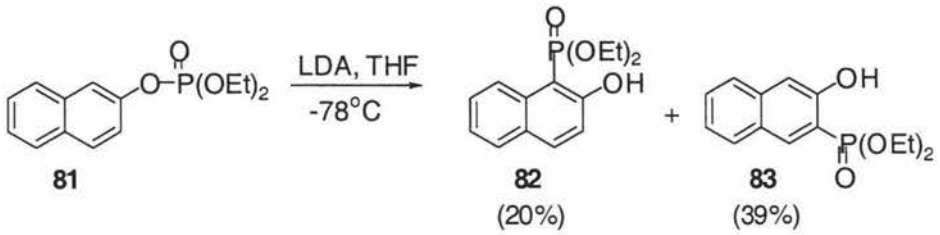
2.6 Naphthol

Dwahan and Redmore extended their work on the rearrangement to the naphthalene ring system.[19] There had previously been only two related examples of such metalation-induced 1,3 migrations reported in the naphthol series. Diethyl 1-naphthyl phosphate underwent clean regioselective rearrangement to diethyl (1-hydroxy-2-naphthyl)phosphonate, with no indication of 1,4-migration of the phosphate group to C8 which had previously been seen by Coll *et al.*[20] This suggests that regioselective lithiation occurs at the 2-position.



Scheme 2.25

It had been reported that 2-naphthol undergoes regioselective lithiation at the 3-position.[20] However, lithiation of diethyl 2-naphthyl phosphate gave a 2:1 mixture of two products, presumably due to lithiation at both positions 1 and 3.



Scheme 2.26

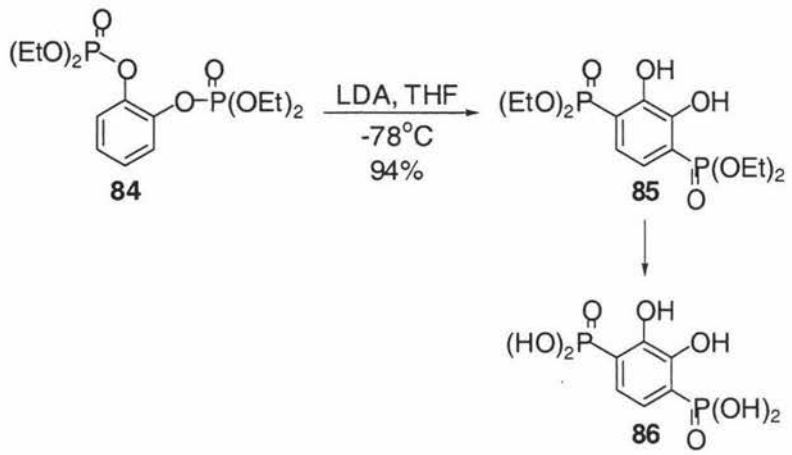
Double and triple migrations on the naphthalene ring system were also carried out on phenylphosphates with yields from 52-65% (see §2.7).

2.7 Multiple rearrangements

A series of papers were published by Dhawan and Redmore extending their observations to multiple rearrangements.

2.7.1 Two phosphates attached to the same aromatic ring:

The first of these papers explored double rearrangements of phosphates to prepare aryl diphosphonic acid derivatives in >80% yields (Scheme 2.27).[7]

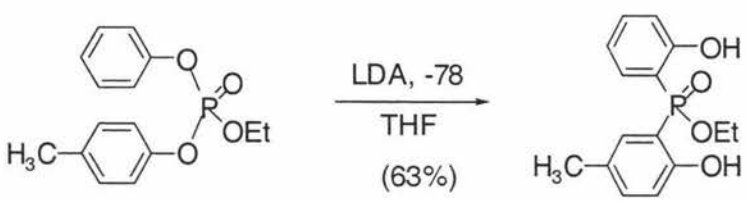


84 85 86

Scheme 2.27

2.7.2 Two aromatic rings attached to the same P:

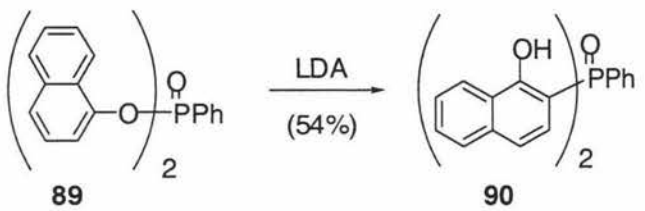
In their next paper they reported the preparation of ethyl *bis*(2-hydroxyaryl)phosphinates using the double migration methodology.[21]



87 88

Scheme 2.28

A similar double rearrangement was seen when di(1-naphthyl)phenylphosphonate was treated with excess LDA (Scheme 2.29).



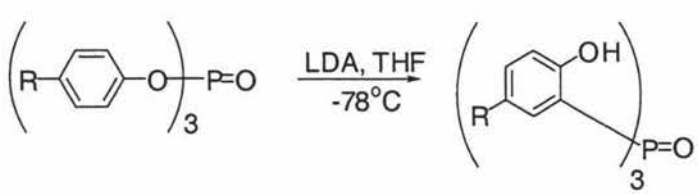
Scheme 2.29

Continuing their interest in the phosphate-phosphonate rearrangement, they reported the rearrangement of diaryl phenylphosphonates to give *bis*(2-hydroxyaryl)phenylphosphine oxides (Scheme 2.30).[22]

Scheme 2.30

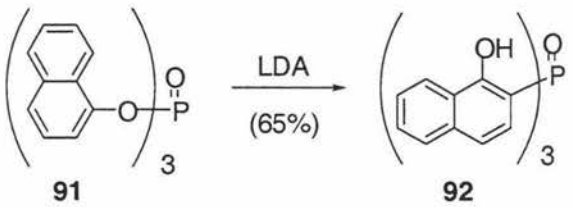
2.7.3 Three aromatic rings attached to the same P:

Based on these studies Dhawan and Redmore suggested that triaryl phosphates might undergo a triple 1,3-migration of phosphorus from O→C. This was achieved successfully with high yields, providing a novel way of preparing *tris(*2-hydroxyaryl)phosphine oxides (Scheme 2.31), which had only been reported once prior to this work.[23]



Scheme 2.31

This was successfully applied to the naphthalene ring system also (Scheme 2.32).

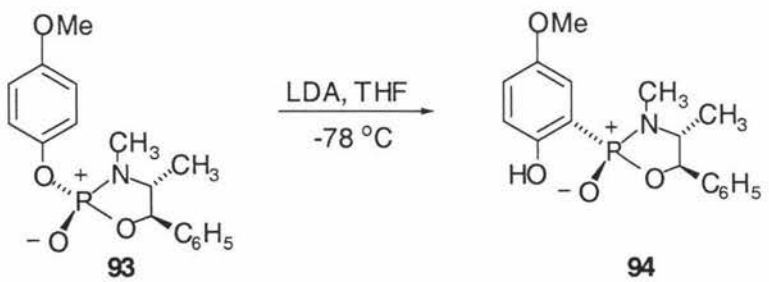


91 **92**

Scheme 2.32

2.8 Stereochemical and mechanistic considerations

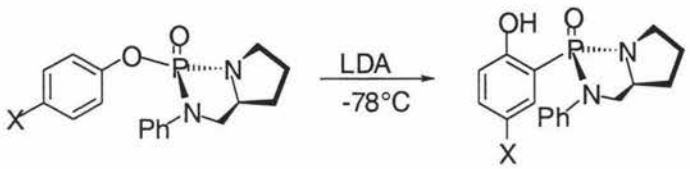
Investigations into the stereochemistry of the rearrangement using 1,3,2-oxazaphospholidine 2-oxides were reported in 1990.[24] The rearrangement of **93** to **94** (Scheme 2.33) occurred with retention of configuration at the phosphorus, impling a concerted migration.



93 **94**

Scheme 2.33

More recently, a total regio- and stereoselective rearrangement was reported to give P-(*o*-hydroxyaryl)diazaphospholidine P-oxides, which are used as catalysts in the asymmetric addition of diethylzinc to aromatic aldehydes (Scheme 2.34).[25]

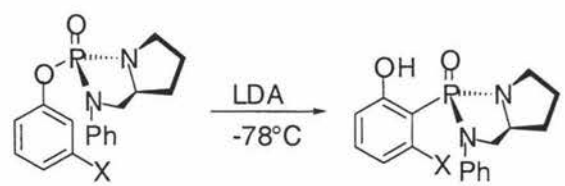


X	Yield (%)
OMe	86%
F	76%
Cl	77%

Scheme 2.34

Reactions of *para*-substituted precursors led exclusively to the expected products with 76-86% yields. The rearrangements all proceeded with total retention of configuration at the phosphorus atom and with complete regioselectivity.

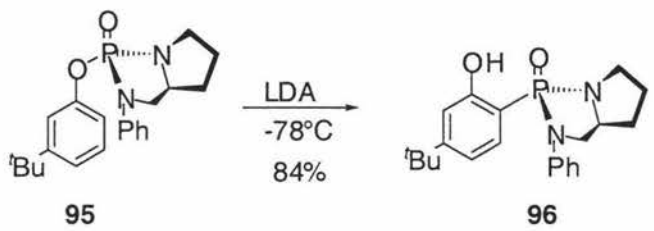
The rearrangement of *meta* substituted compounds also all proceeded with 100% retention of configuration, in high yields (Scheme 2.35). In these three cases the formation of a single regioisomer was attributed to the combined *ortho*-orienting character of the MeO, F and Cl, groups with the phosphoryl group.



X	Yield (%)
OMe	72
F	85
Cl	92

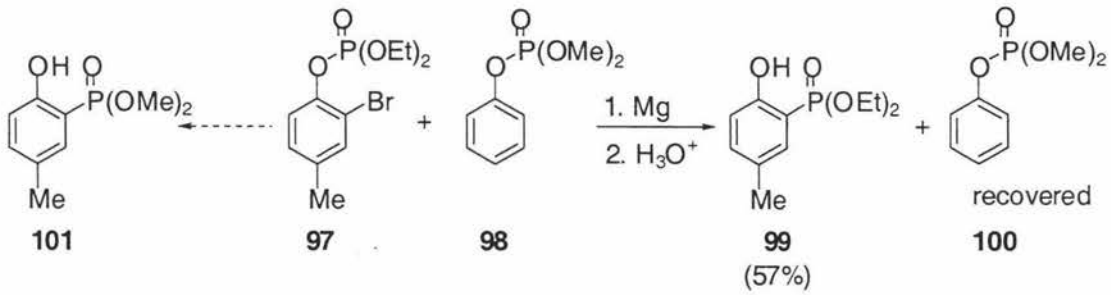
Scheme 2.35

On the other hand, the significant steric hindrance of the *tert*-butyl group, directed rearrangement of compound **95** in the opposite direction, with complete regioselectivity.



Scheme 2.36

Heinicke *et al.* demonstrated that the rearrangement was intramolecular using the crossover experiment depicted in Scheme 2.37.[6] Generation of the anion from aryl bromide **97**, in the presence of phosphate **98**, gave a reasonable yield of the product **99**, arising from intramolecular rearrangement. If the anion derived from **97** had the opportunity to attack the methyl phosphate in compound **98**, the crossover product **101** would have been observed.

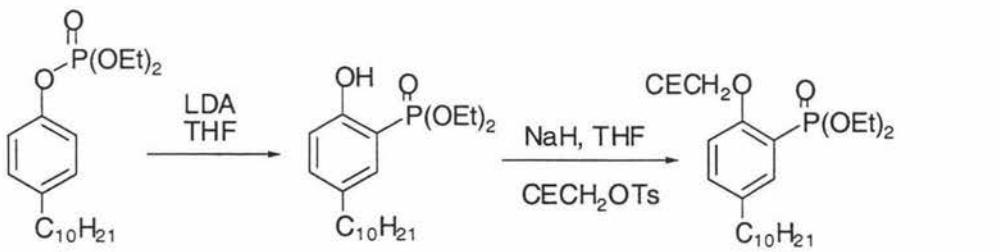


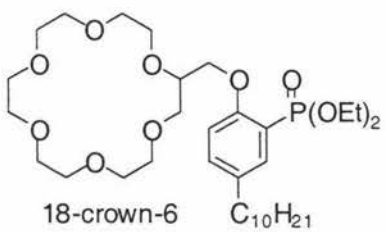
Scheme 2.37

2.9 Applications in complex molecules

The synthesis of lipophilic crown ethers with pendant phosphonic acid groups was published in 1992.[26] Such crown ethers containing pendant proton-ionizable groups are useful for solvent extraction, liquid surfactant, polymer-supported liquid membranes and

transport of alkali metal cations. The pendant phosphonic acid groups have greater acidity than carboxylic acid analogues, and also provide di-ionizable ligands. Czech *et al.* used two different routes to synthesis these molecules; the second more direct method employed the rearrangement. (Scheme 2.38). This allowed them to investigate the influence of crown ether ring size upon the efficiency and selectivity of alkali metal cation extraction and liquid membrane transport.





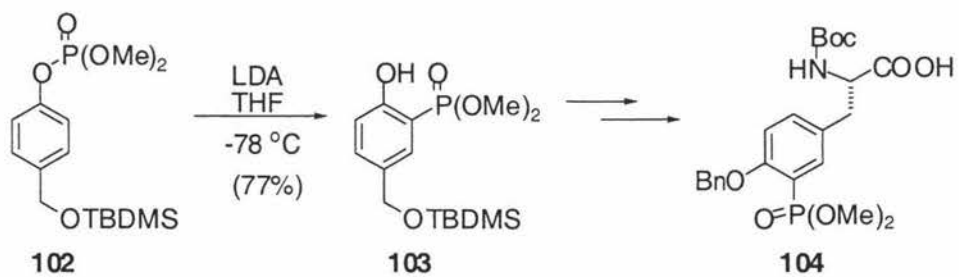
No	Crown ether	Yield (%) step 1
1	15-Crown-5	61
2	18-Crown-6	71
3	21-Crown-7	61
4	24-Crown-8	69

Scheme 2.38

The desired crown ether was coupled as a tosylate to the phenoxide ion to give the lipophilic crown ether diethyl phosphonates.

Paladino *et al.* utilized the rearrangement in the synthesis of phosphotyrosine analogues.[27] Peptides incorporating such an amino acid could serve as product inhibitors of kinases, or substrate inhibitors of phosphatases, and thus have potential as anticancer drugs.

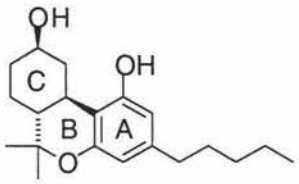
Phosphotyrosine is easily hydrolysed under acidic conditions, so this paper reported the synthesis of several analogues with stable C-P bonds (*c.f*, the labile C-O-P linkage). The rearrangement failed when attempted directly on protected tyrosine, so they prepared the 2-hydroxyarylphosphonate moiety separately (Scheme 2.39). Anion induced rearrangement of **102** gave **103** which was converted to protected amino acid building block **104**.



102 **103** **104**

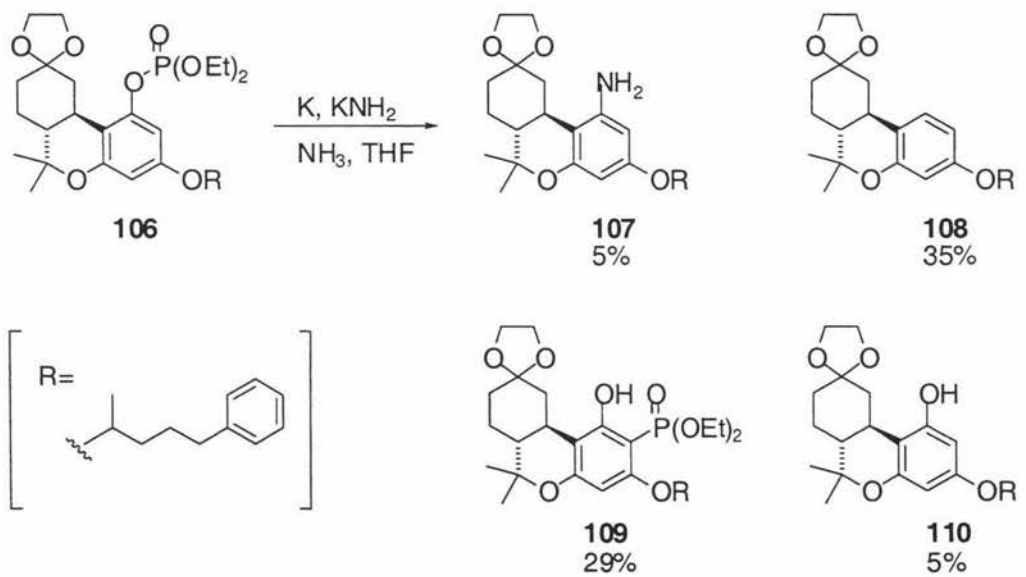
Scheme 2.39

In 1990, Melvin *et al.* published the synthesis of a new series of 9-nor-9β-hydroxyhexahydrocannabinoids (*e.g.*, compound **105**), a family of compounds with potent analgesic properites without opiate effects (*i.e.*, painkiller without being addictive).[28]



105

In particular Melvin was investigating the importance of the phenol in the aromatic A-ring for receptor recognition. The reaction of aryl phosphate esters with potassium amide and potassium metal had been reported as a mild method for the transformation of phenols to anilines. However, Melvin *et al.* obtained a very low yield of aniline **107** along with the reduction product **108**, compound **109** arising from rearrangement, and **110** from nucleophilic attack at phosphorus (Scheme 2.40).



Scheme 2.40

2.10 Summary

The anionic phospho-Fries rearrangement has been shown to be an effective synthetic tool for the formation of arylphosphonates.

A variety of substituents at phosphorus has been investigated. Deprotection to give free phosphonic acids, where required, is a major consideration. Steric and electronic effects have been shown to play a role in the ability of the phosphorus group to migrate.

It can be concluded that both the electronic and steric nature of the substituents on the aromatic ring appear to have a direct influence on the success of rearrangement and the two probably need to be considered together in predicting the regiochemical outcome of a rearrangement.

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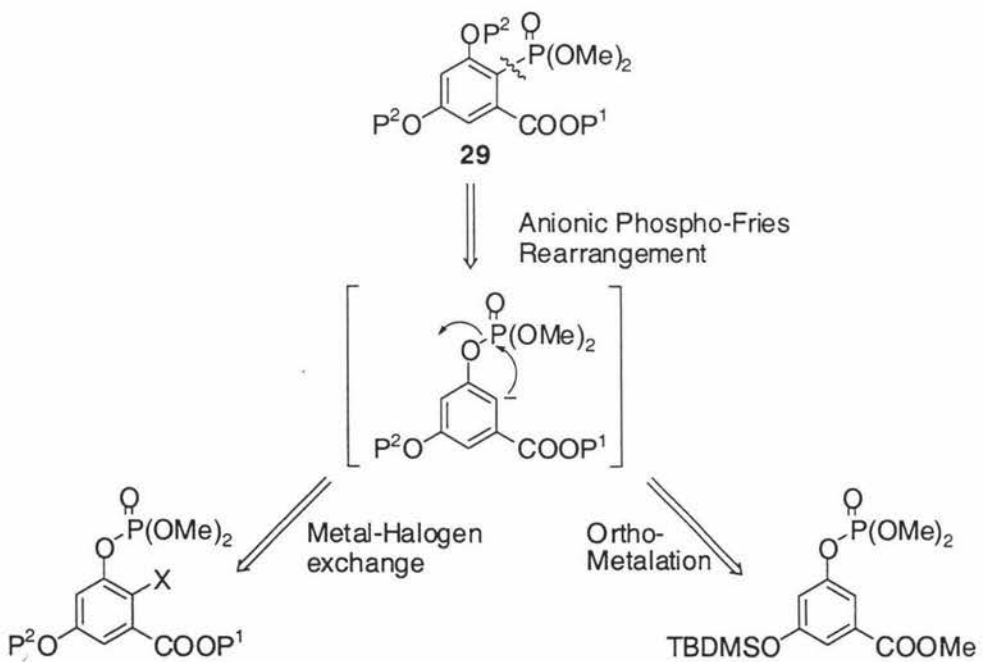
3. SYNTHETIC APPROACHES TO THE AROMATIC FRAGMENT OF HAPTEN 26

3.1 Route A: Protection of the Phenols as *tert*-Butyldimethylsilyl Ethers.

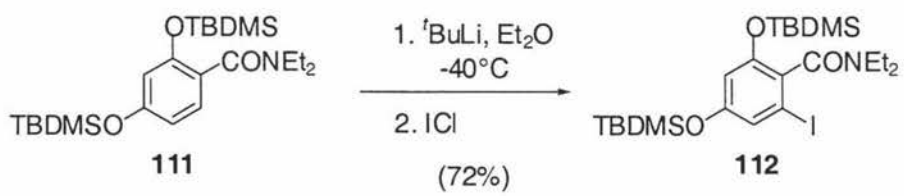
Retrosynthetic analysis of our hapten led to aromatic fragment **29**. Further retrosynthetic analysis of this target is shown in Scheme 3.1. We envisioned that compound **29** could be derived from resorcylic acid (**36**), capitalizing on the novel anionic-phospho Fries rearrangement to establish the C-P phosphonate bond.



Scheme 3.1: Retrosynthetic analysis of aromatic fragment

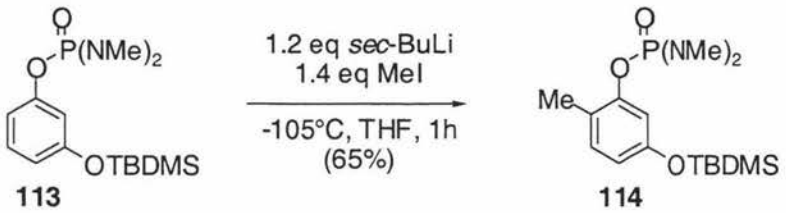
Since the production of the hapten might ultimately need to be viable on an industrial scale, we looked to use inexpensive starting materials and reagents and also to limit the number of steps in the synthetic sequence. For this reason we chose to use direct *ortho*-metalation, as metal-halogen-exchange necessitates the introduction of bromine which requires extra steps in the synthesis. As the substituents on the aromatic ring are known to have a direct effect on the success of the rearrangement of the phosphate, the choice of phenol protecting group was considered carefully. It had to be stable to the rearrangement conditions (*i.e.*, strong base) as well as provide steric hindrance to allow regioselective deprotonation of the aromatic ring.

Kalivretenos *et al.* employed the hindered *tert*-butyldimethylsilyl (TBDMS) ether to prevent *ortho* lithiation between the two phenols in compound **111**.[1] The TBDMS group was stable to the strong base (*tert*-BuLi) and demonstrated the steric hindrance required.



Scheme 3.2

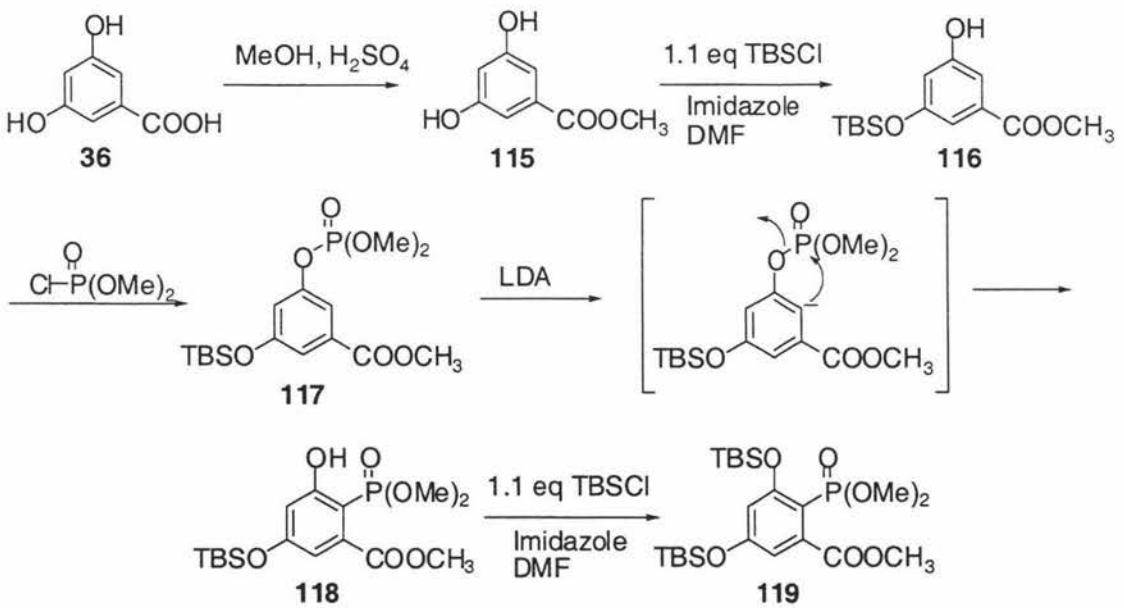
Another example from the literature which demonstrated *ortho*-metalation away from the bulky TBDMS group is given below.[2] Watanabe *et al.* were able to methylate regioselectively at very low temperatures.



113 114

Scheme 3.3

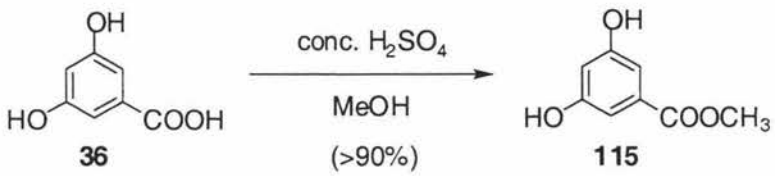
Thus, we chose to use a TBDMS ether as our phenol protecting group. We elected to protect the acid as a methyl ester and proposed synthetic route A (Scheme 3.4), consisting of only five steps. In terms of the regioselectivity of the *ortho*-metalation, we hoped that the COOMe functionality of compound **117** would increase the relative acidity of the adjacent Ar-H. The ester also has the potential to coordinate. These combined factors made us optimistic that the rearrangement would occur in the desired direction to give **118**. Protection of the free phenol as its TBDMS ether would give **119**.



36 115 116 117 118 119

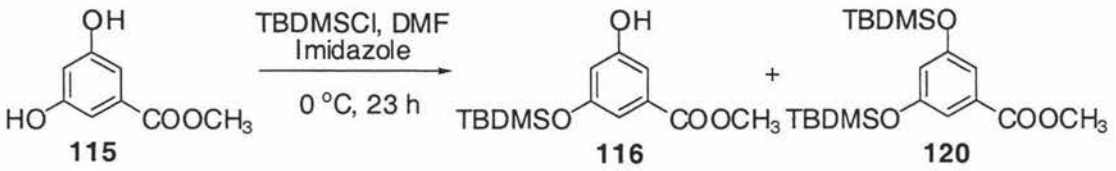
Scheme 3.4

Protection of the acid as its methyl ester was achieved by heating at reflux in methanol under acidic conditions (Scheme 3.5). Evidence for methyl ester formation was obtained from the NMR spectra of the product. The $COO\underline{CH_3}$ group gave rise to a singlet at δ 3.85 in the ^1H NMR spectrum and a signal at δ 52.5 in the ^{13}C NMR spectrum.



Scheme 3.5

Protection of one of the two free phenols as a TBDMS ether was attempted according to Miller,[3] who reported a 62% yield for this reaction. A significant amount of di-silylated compound, **120**, was also obtained. In our hands, a 40% yield of the silyl ether **116** was obtained with ~50% of unreacted starting material recovered. Based on the masses reported in their experimental procedure, we calculated that the yield of **116** obtained by Miller was only 49%.



	Compound **116**	Compound **120**
Reported	62	22
Calculated	49	17
Current	40	<10%

Scheme 3.6

The incorporation of the TBDMS group was confirmed by a singlet at δ 0.20 [$Si(CH_3)_2$] and one at δ 0.98 [$SiC(CH_3)_3$] in the ^1H NMR spectrum. Due to the decrease in the symmetry of the molecule, the aromatic region featured two doublets of doublets, as well as an apparent triplet signal (Figure 3.1).

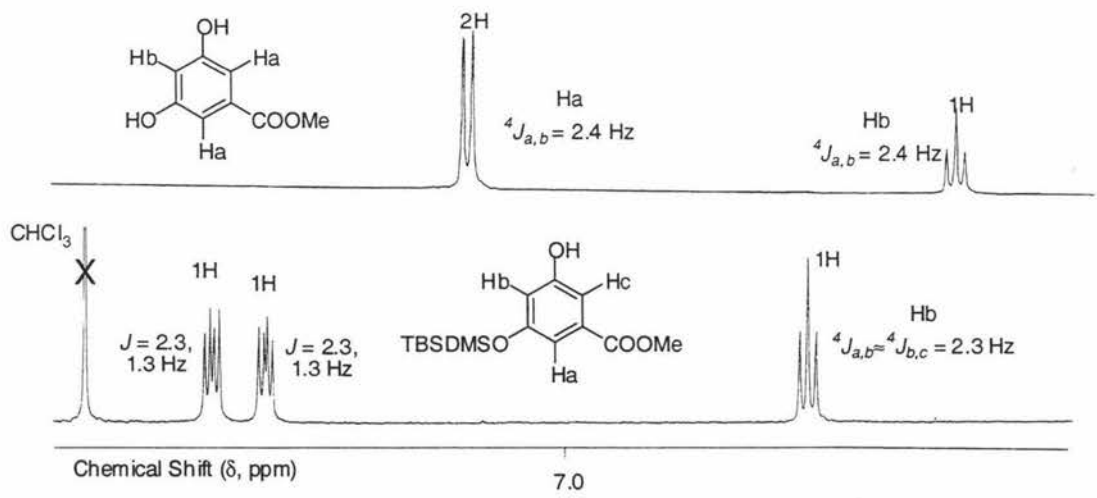


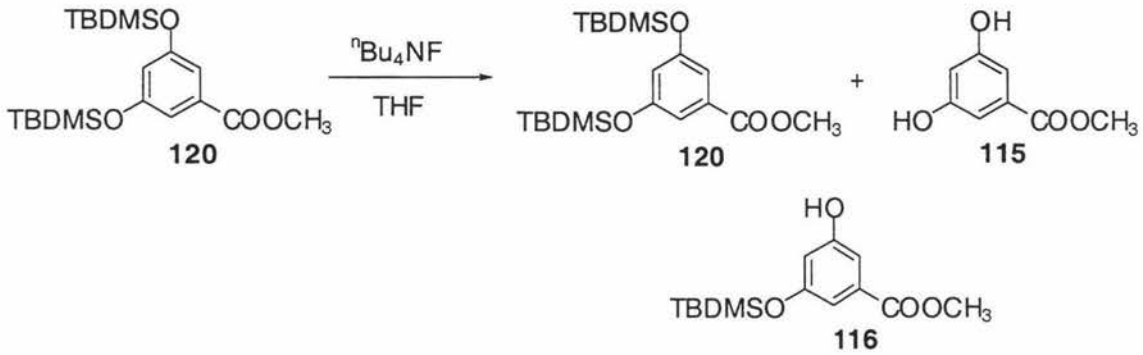
Figure 3.1 ^1H NMR of compound **115** (in CD_3OD) and compound **116** (in $CDCl_3$) at 270 MHz.

Our attempts to improve this mono-silylation reaction are summarised in Table 3.1. We hoped that the production of a mono-phenolate anion (Entries 4 and 5) would engender a superior nucleophile, thereby improving the yield of the monoprotected product. We also investigated protection using the *tert*-butyldiphenylsilyl ether (Entry 5), a bulkier protecting group, which we hoped might be more discriminating.

Table 3.1 TBDMS protection of compound **115**.

Entry	R_3SiCl (equiv.)	NaH (equiv.)	Imidazole (equiv.)	Time (h)	Yield of **116** (%)
1	TBDMSCl (1.1)	0	1.1	20	40
2	TBDMSCl (1.1)	0	1.1	3	40
3	TBDMSCl (1.1)	0	1.5	48	53
4	TBDMSCl (1.1)	1.1	1.1	23	44
5	TBDPSCl (1.1)	1.1	1.1	4	26

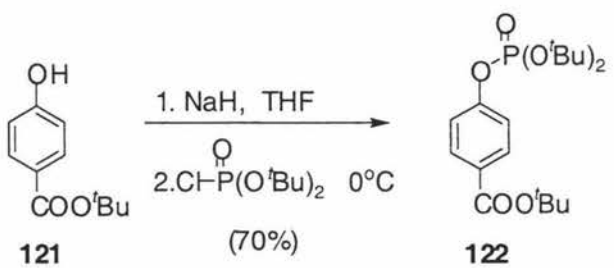
It seemed impossible to prevent the formation of the disilylated product **120**, so we considered the selective removal of one TBDMS group from **120** as an alternative approach. This was attempted using TBAF, and resulted in a mixture of starting material **120**, desired product **116**, and some of the compound **115**, reflecting the loss of both silyl ethers (Scheme 3.7).



Scheme 3.7

In summary, the best results for the preparation of monosilyl ether (~50% yield of **116**) were obtained under standard, neutral conditions (Entries 1-3 in Table 3.1).

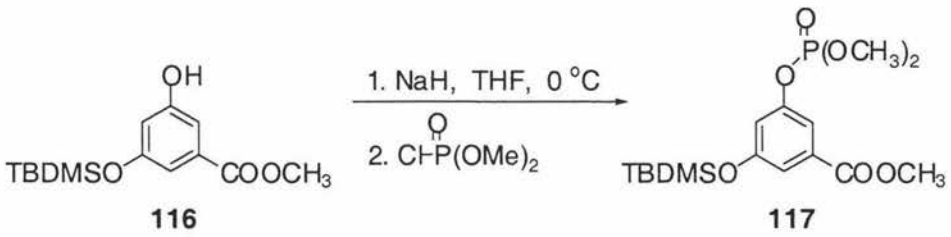
The next step in the synthesis involved the phosphorylation of the free phenol, which was expected to proceed in good yield based on literature precedent.[4] The following example illustrates phosphorylation of a phenol bearing an ester substituent in the *para* position.



Scheme 3.8

We generated the phenolate anion, as recommended by Casteel,[4] adding the chlorophosphate and stirring for 72 hours in the cold room. Under these conditions, we

obtained a mixture of products and only poor yields of the desired product **117** (Scheme 3.9).



116 **117**

Scheme 3.9

Table 3.2: Phosphorylation of phenol **116**

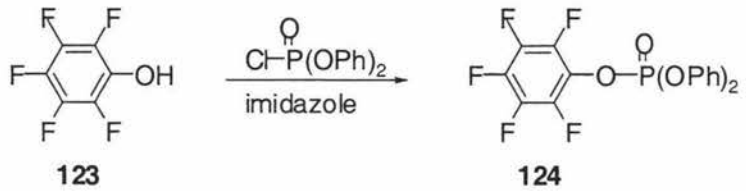
Time	Yield **117**
72 h	<10%
3 h	18%
2 h	39 %
20 min	42%

This reaction was attempted several times, varying the reaction time, in efforts to optimize the yield. The shortest time gave the best results: a 42% yield when the reaction was quenched after only 20 minutes. This was still a disappointing result, in comparison to the high yields reported by Casteel.[4]

We explored two alternative phosphorylation conditions:

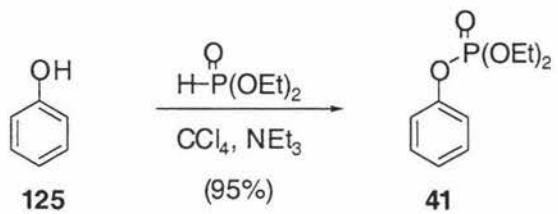
A. Imidazole in dichloromethane had previously been used in the phosphorylation of pentafluorophenol (**123**), to produce the peptide coupling reagent **124** (Scheme 3.10).[5] Five electron-withdrawing fluorine substituents on the ring make this phenol a much poorer

nucleophile than our own phenol **116**. This reaction made us optimistic that these conditions would work for our substrate.



Scheme 3.10

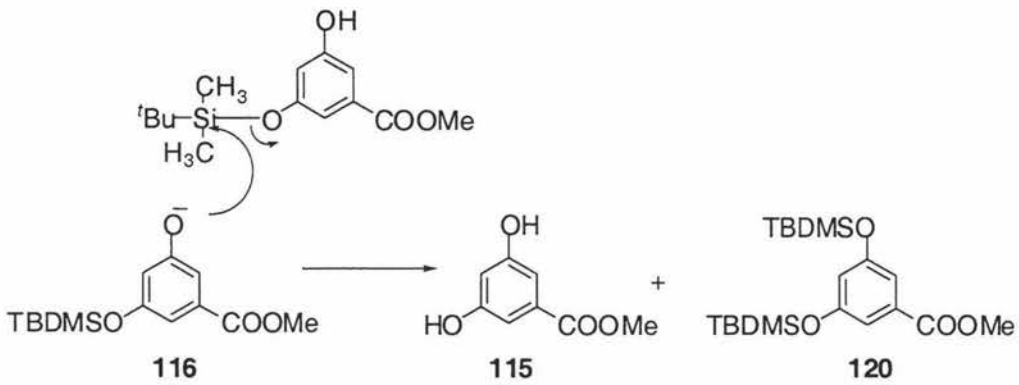
B. The phosphorylation was also attempted following a procedure by Kenner and Williams, but substituting dichloromethane for carbon tetrachloride.[6]



Scheme 3.11

Unfortunately, both conditions gave only low yields (<10%) of the desired phosphorylated product **117**. Small amounts of two by-products were examined and identified by NMR and mass spectrometry. They were revealed to be disilylated compound **120** and the desilylated methyl resorcylate **115**.

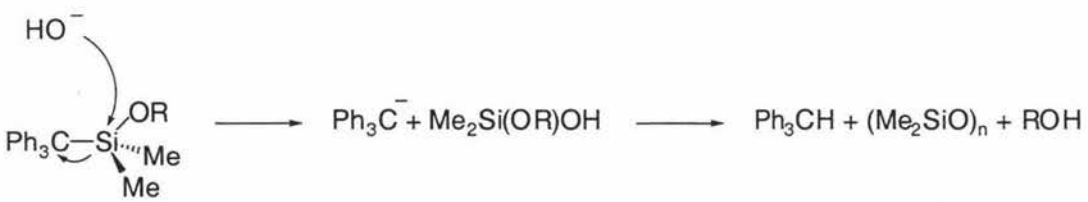
This revelation led to the hypothesis that the TBDMS protecting group is unstable in the presence of a phenolate anion. A pseudo-disproportionation reaction is possible, as illustrated Scheme 3.12.



Scheme 3.12

This explained the formation of the observed by-products in the phosphorylation reaction, which on closer inspection were identified as compound **115** and compound **120**. It also explained our inability to improve the yield of **116** in the TBDMS protection reaction, via anion formation (Table 3.1).

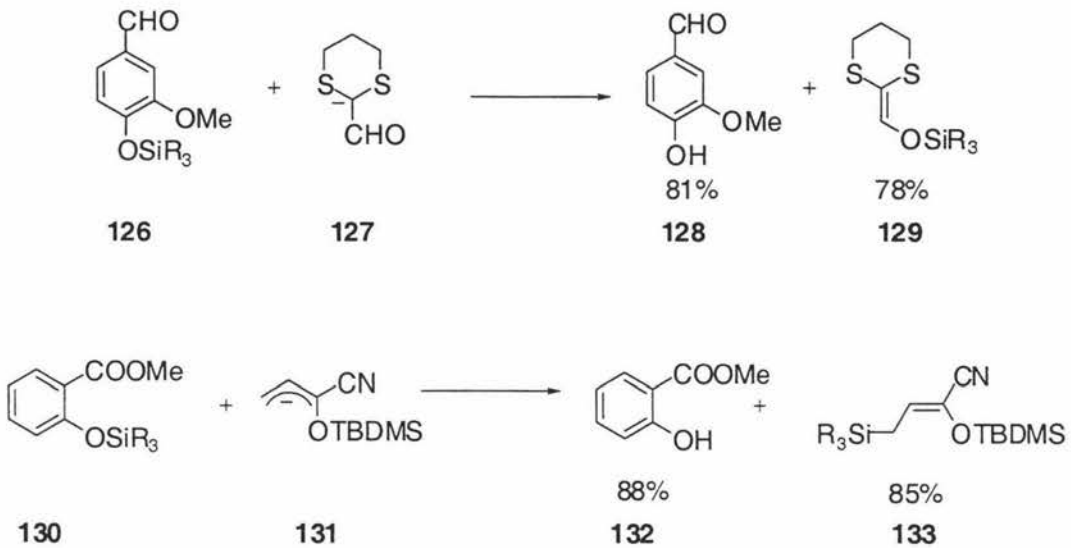
There is some precedent for the instability of trityldimethylsilyl ethers to base (Scheme 3.13).[7] However, this was attributed to the highly stabilized trityl carbanion being a good leaving group.



Scheme 3.13

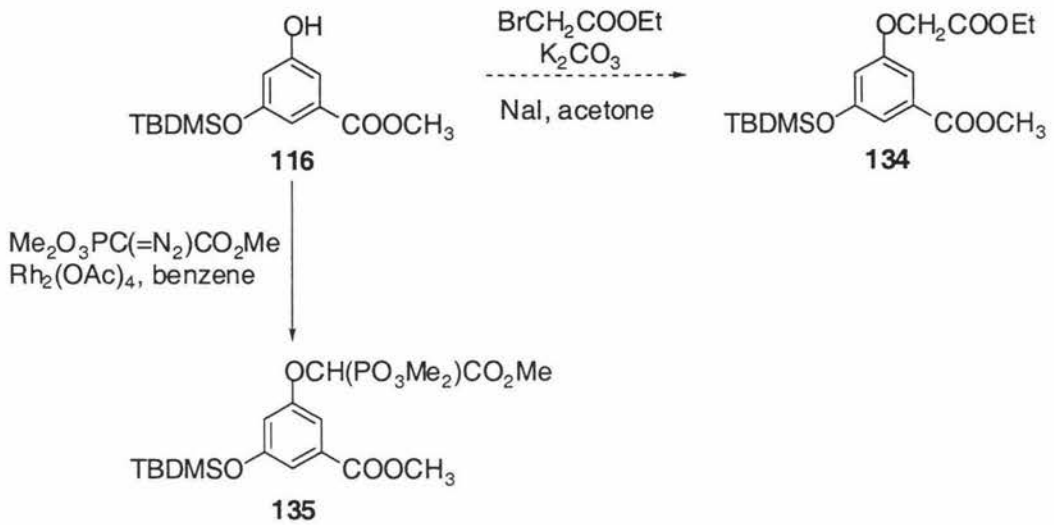
The trityldimethylsilyl ether is easily removed using K_2CO_3 in methanol, or under standard conditions employing tetrabutyl ammonium fluoride, and showed greater stability to acid than the TBDMS protecting group.

There is also a report of TBDMS being susceptible to cleavage by stabilized carbanions and oxyanions (Scheme 3.14).[8] This weakness of the O-Si bond was attributed to the presence of electron withdrawing groups in conjugated locations.



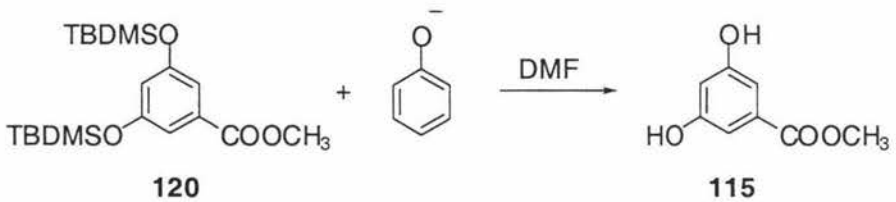
Scheme 3.14

Miller also commented that TBDMS was an ineffective protecting group under standard conditions for phenol alkylation. They instead achieved this transformation via a rhodium acetate-catalysed coupling with an α-diazoester (Scheme 3.15).[3]



Scheme 3.15

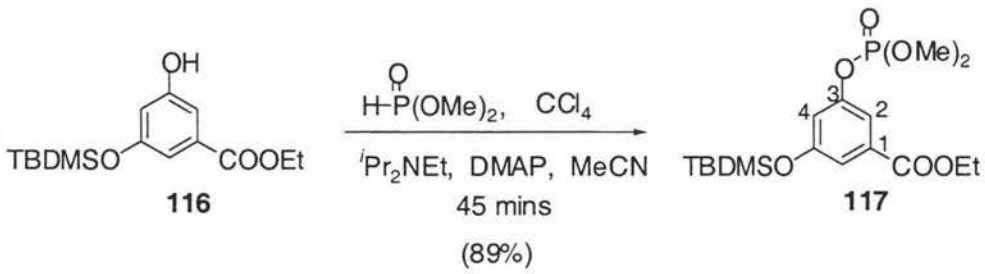
To confirm the origin of the instability of our TBDMS protecting group to the phenolate anion, we took compound **120** and treated it with sodium phenolate. All of the starting material disappeared, confirming that the TBDMS group is indeed unstable to these conditions.



Scheme 3.16

It was therefore necessary to prepare phosphate **117** under non-basic conditions, to preserve the integrity of the TBDMS protecting group. A well-established method for phosphate formation is the Atherton-Todd procedure.[9] First introduced by Atherton and Todd, in the

context of oligonucleotide chemistry, it involves generation of the chlorophosphate *in situ* from the appropriate dialkyl phosphite and carbon tetrachloride.



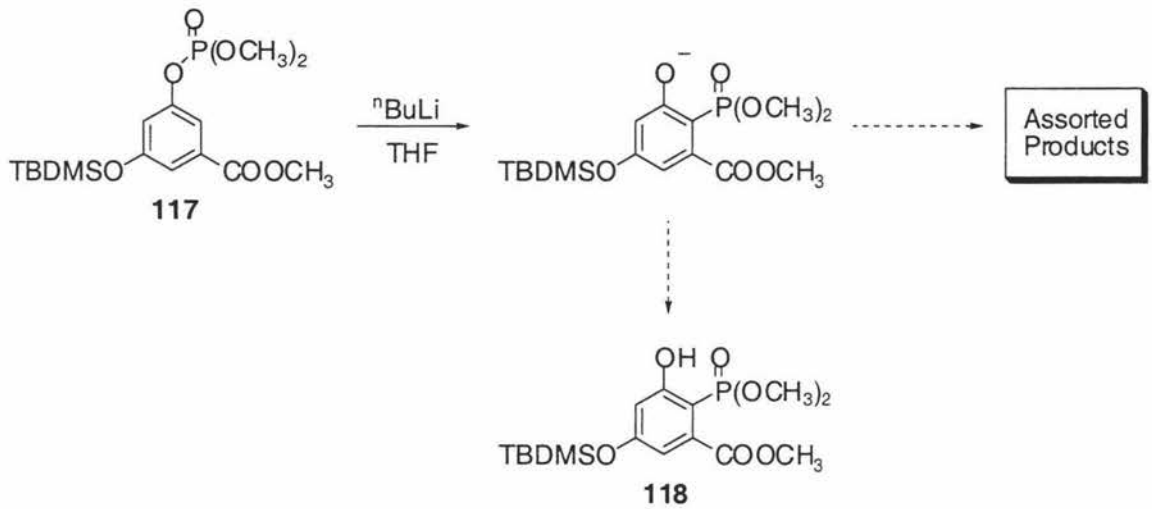
Scheme 3.17

The original Atherton-Todd procedure used carbon tetrachloride as the solvent, but changing the solvent to acetonitrile and using 5 equivalents of carbon tetrachloride, as reported by Silverberg,[10] gave a higher yield and minimised the use of carbon tetrachloride. The phosphate product **117** showed a doublet at δ 3.88 in the ^{1}H NMR and a doublet at δ 54.9 (J = 6 Hz) in the ^{13}C NMR corresponding to the $PO(OCH_3)_2$ group. This confirmed the successful phosphorylation reaction. Coupling of the ^{31}P nucleus to C2, C3 and C4 of the aromatic ring was also observed.

In summary, we produced our substrate in three steps and 40% overall yield. While the monosilylation remained unsatisfactory (~50% yield), the overall preparation of methyl 3-dimethylphosphate-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]benzoate (**117**) was efficient.

The anionic phospho-Fries rearrangement of substrate **117** was investigated briefly (Scheme 3.18). It led to a complex mixture of products that had lost functional groups:

destruction of the carboxylate ester, phosphate and TBDMS ether was recognized in various products. We could not detect the desired rearranged product. The unfortunate reality was that, following rearrangement, a phenolate anion is generated in the reaction mixture. As established earlier, the TBDMS protecting group is fragile in the presence of such a species.

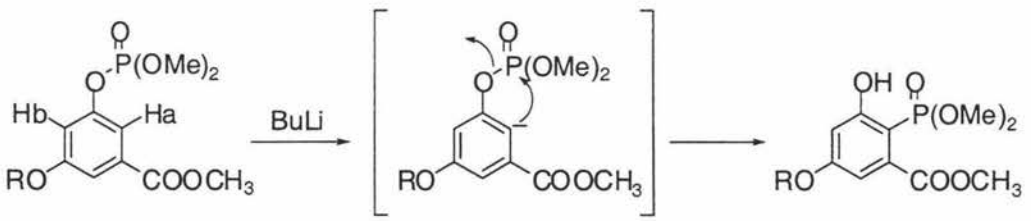


Scheme 3.18

Thus, while our initial choice of the TBDMS group was well precedented a new protecting group was required, that was stable to phenolate anions and would provide the same steric hindrance as TBDMS.

3.2 Route B: Temporary Protection of Phenols as Benzyl Ethers

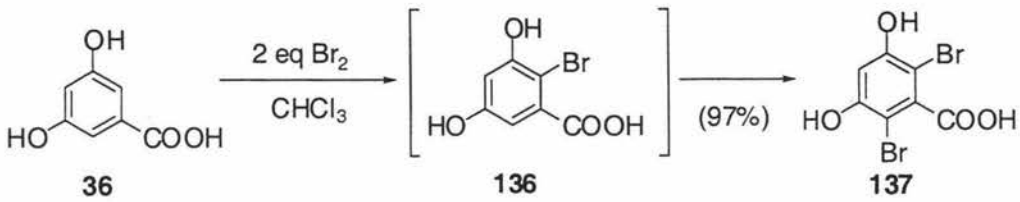
Our primary goal in the new approach was to find a phenol protecting group which would withstand the reaction conditions throughout the sequence. Another pitfall of route A was the reliance on regioselective deprotonation of the aromatic ring (Scheme 3.19). Even if we could find a suitable replacement for the TBDMS group, this ambiguity would remain.



Scheme 3.19

In our revised route we therefore wanted to incorporate halogen-metal exchange into our strategy, to ensure anion generation at the desired position. To achieve this, regioselective bromination of our aromatic ring was required to install the halogen between the phosphate and methyl ester substituents.

There are several examples of the bromination of α-resorcylic acid derivatives in the literature. Borchardt reported dibromination of α-resorcyclic acid itself in 97% yield (Scheme 3.20).[11] We hoped that treatment of the acid with one equivalent of bromine would give us a monobrominated product.

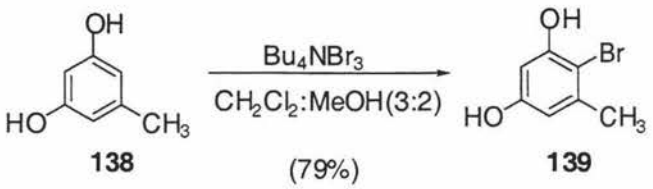


Scheme 3.20

With the installation of one electron-withdrawing bromine substituent, 2-bromo-3,5-dihydroxybenzoic acid (**136**) should be less reactive toward electrophilic aromatic substitution than α-resorcylic acid (**36**), making the formation of 2,6-dibromo-3,5-dihydroxybenzoic acid (**137**) unlikely in the presence of a single equivalent of bromine. Unfortunately, a mixture of mono- and dibrominated products was obtained. These proved very difficult to separate, due to their polar nature.

We also attempted bromination of methyl ester **115** under similar conditions, with similar results. We thought that the monobrominated product could be more soluble than the starting material and that this might explain the appearance of dibrominated material. We reasoned that increasing the solubility of the starting material would give us better results. We changed the solvent to ethanoic acid,[12] and also conducted the reaction in methanol treated with sulphuric acid.[13] None of these modifications led to noticeable improvements.

Tetrabutyl ammonium tribromide has been shown to be a useful, stable reagent for the mono, *para*-bromination of phenols.[14] For example orcinol (**138**) was converted to 2-bromo orcinol (**139**) in good yield (Scheme 3.21).

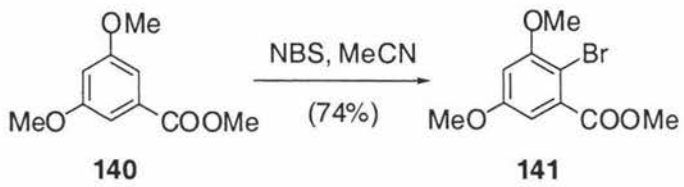


138 **139**

Scheme 3.21

Our attempts to reproduce this reaction on orcinol itself, and extend it to other substrates such as methyl ester **115** and α-resorcylic acid (**36**), were unsuccessful, with only starting material recovered from each reaction. This suggested a problem with our reagent which was new from Alfa Aesar.

N-Bromosuccinimide (NBS), has been widely used in the bromination of aromatic rings, for example the following reaction was reported by Lee *et al.*[15]



140 **141**

Scheme 3.22

The mechanism of bromination by NBS was demonstrated by Dauben and McCoy.[16] The reaction is initiated by small amounts of Br• abstracting hydrogen from the substrate.

Step 1

Step 2 $Br\bullet + RH \rightarrow R\bullet + HBr$

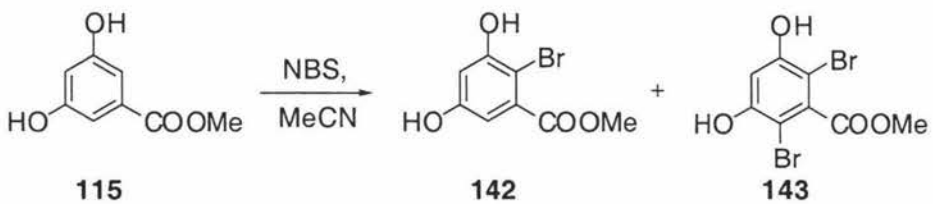
Step 3

Step 4 $R\bullet + Br_2 \rightarrow RBr + Br\bullet$

Scheme 3.23

Thus, the function of the NBS is to provide a steady source of Br_2 in a concentration low enough to prevent di-bromination.

We followed the procedure described by Lee,[15] with methyl ester **115** as the substrate. This again gave poor yields of the di- and mono-brominated products as well as starting material (Scheme 3.24).



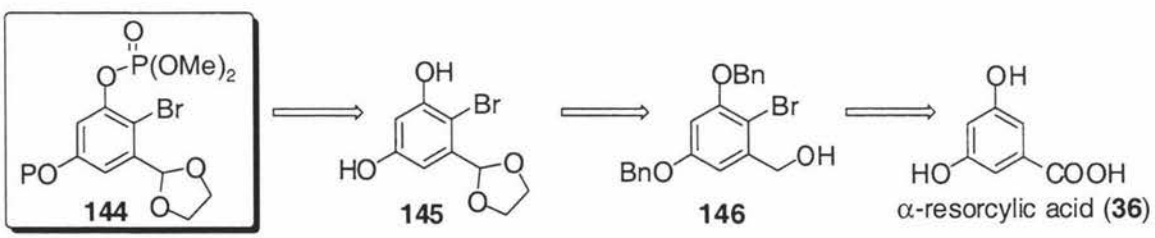
Scheme 3.24

Looking through the literature, successful bromination of phenolic substrates with NBS requires prior protection of the phenols. This is probably a consequence of the mechanism

involving free radicals. As phenols themselves are readily converted to stable free radicals, they are incompatible with the bromination conditions.

The protection of the phenols as methyl ethers has been widely adopted. However, the removal of this protecting group often requires harsh conditions. We therefore sought an alternative.

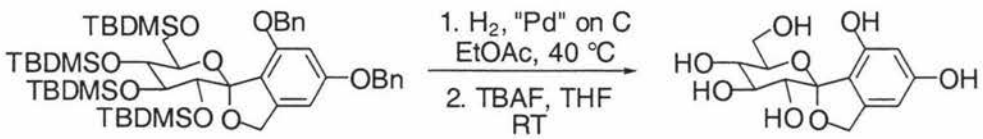
Our proposed target was **144** and its retrosynthetic analysis is illustrated in Scheme 3.25. Compound **146** has been prepared and utilized several times, most notably in the synthesis of *C*–arylglucosides of the papulacandin type.[17] We felt that it would be a useful intermediate in the synthesis of **144**. Benzyl ethers were therefore chosen to serve as temporary phenol protecting groups.



Scheme 3.25 Retrosynthetic analysis of proposed aromatic fragment

We hoped that we would be able to differentiate between the two phenols in **145** due to the presence of the bulky bromine. We took advantage of this reassessment of our target, to incorporate a protected aldehyde (*c.f.,* methyl ester in Route A). Only one step would then be required to liberate the aldehyde prior to the final Horner-Emmons cyclization. The aldehyde protecting group needed to be stable to hydrogenation and also be able to be

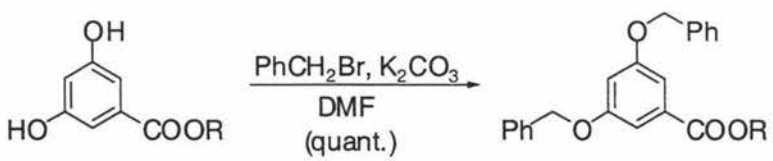
selectively removed in the presence of other protecting groups for the amalgamation of the two major fragments **29** and **30** (see § 1.5). Friesen and Sturino demonstrated the stability of acetals to hydrogenation conditions (Scheme 3.26).[17] Thus, the acetal was chosen as the protecting group for the aldehyde.



147 **148**

Scheme 3.26

The first step in this synthesis was the protection of the phenols as benzyl ethers.[18] The benzylation was initially performed on the methyl ester **115**, and then on α-resorcylic acid itself (**36**), which led to simultaneous protection of the acid functionality as its benzyl ester, thereby eliminating a step from the sequence. Both benzylation reactions proceeded in quantitative yield. Incorporation of the benzyl groups was confirmed by additional signals in the aromatic region of the ^{1}H NMR spectra, and benzylic CH_2 protons gave rise to signals around δ 5 ppm.

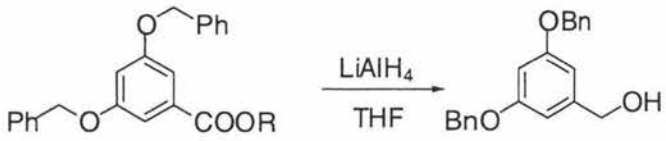


36 R = H
115 R = Me

149 R = Bn
150 R = Me

Scheme 3.27

The next step involved the reduction of the ester functionality to give the benzyl alcohol, with $LiAlH_4$, in quantitative yields (Scheme 3.28). A significant difference between these two reactions was the by-product of the reduction of the ester: benzyl alcohol in the case of **149** and methanol in the case of **150**. Benzyl alcohol was difficult to separate from the product and so the methyl ester **150** was the preferred precursor to **151**. Although the synthesis of **151** thereby involved three steps, the yields were all quantitative with minimal purification. The identity of compound **151** was confirmed by the disappearance of the ester carbonyl (δ 167) in the ^{13}C NMR spectrum and the appearance of signals due to the new benzylic alcohol: δ 4.61 (^1H NMR) and δ 65.2 (^{13}C NMR).



149 R = Bn
150 R = Me

151

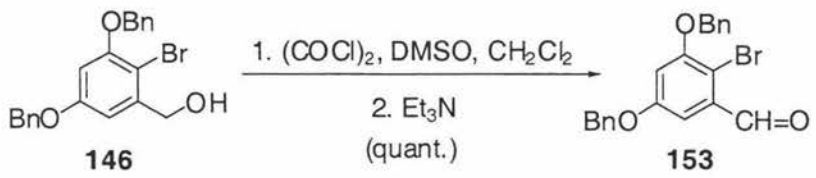
Scheme 3.28

Monobromination was then achieved uneventfully with NBS using Lee's conditions (Scheme 3.29). The formation of the desired regioisomer was confirmed by ^1H NMR. The ^1H NMR spectrum indicated that there was one less proton in the aromatic region relative to the starting material. The two mutually *meta*-coupled protons on the aromatic ring gave rise to doublets at δ 6.55 and 6.81 (J = 2.6 Hz). If the other regioisomer (**152**) was formed, the compound would be symmetrical and thus only one aromatic signal would appear. The regioselectivity of this reaction is due to the strong directing effect of the benzyl ether groups combined with the steric hindrance they create at the position between them.

151 146 152

Scheme 3.29

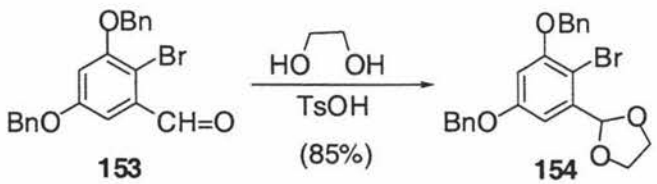
The benzylic alcohol was oxidised to the corresponding aldehyde via a Swern oxidation in quantitative yield (Scheme 3.30). A signal at δ 10.43 in the ^{1}H NMR spectrum confirmed the presence of an aldehyde, as did the carbonyl signal at δ 191.7 in the ^{13}C NMR spectrum.



146 153

Scheme 3.30

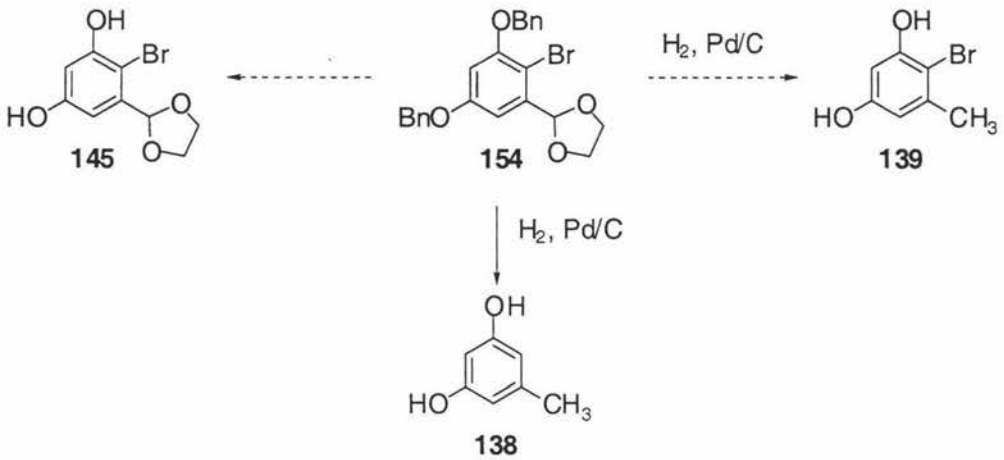
Protection of the aldehyde as a cyclic acetal was achieved by heating at reflux in toluene with ethylene glycol under acidic conditions.[19] The formation of compound **154** was confirmed by the ^{1}H and ^{13}C NMR spectra, with the disappearance of the aldehyde signals and the appearance of a singlet at δ 6.19 due to the acetal proton in the ^{1}H NMR.



153 154

Scheme 3.31

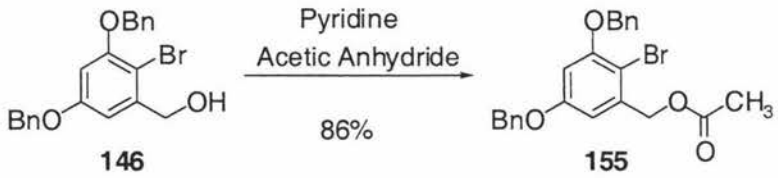
We next needed to remove the benzyl ethers to give compound **145**, and differentiate between the two resulting phenols. We hoped that the electron withdrawing nature and the steric bulk of the bromine would facilitate this. Unfortunately, exposure of compound **154** to hydrogen and Pd/C resulted in reductive cleavage of the benzylidene acetal, leaving us with what we thought was compound **139** (Scheme 3.32). It was surprisingly difficult to isolate and insoluble in most NMR solvents.



Scheme 3.32

The mass spectrum of the crude product mixture appeared to indicate a molecular ion cluster with ions at m/z 202 and 204 in a 1:1 ratio corresponding to the molecular formulae of compound **139**. This was misleading, and emphasises that mass spectrometry provides information about identity, not purity. Retrospectively, it seems likely that **139** was a minor component in the product mixture. The base peak at *m/z* 124 in fact represents M^+ of the major component (orcinol, **138**) in the mixture. Orcinol (**138**) arises from the cleavage, not only of the benzyl ethers and the benzylidene acetal, but of the aryl-bromide bond.

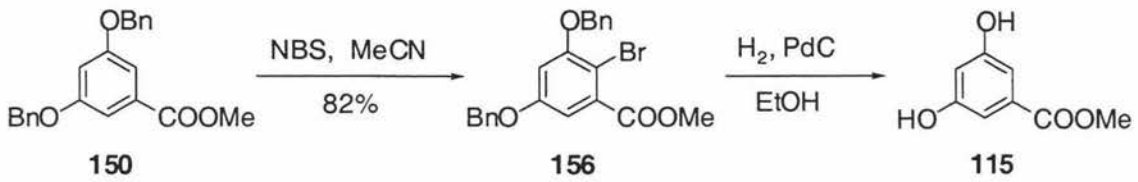
Unaware of the aryl-bromide cleavage, and focussing on the problem of the acetal protecting group, we protected the benzyl alcohol it as its acetate ester **155** (Scheme 3.33).



Scheme 3.33

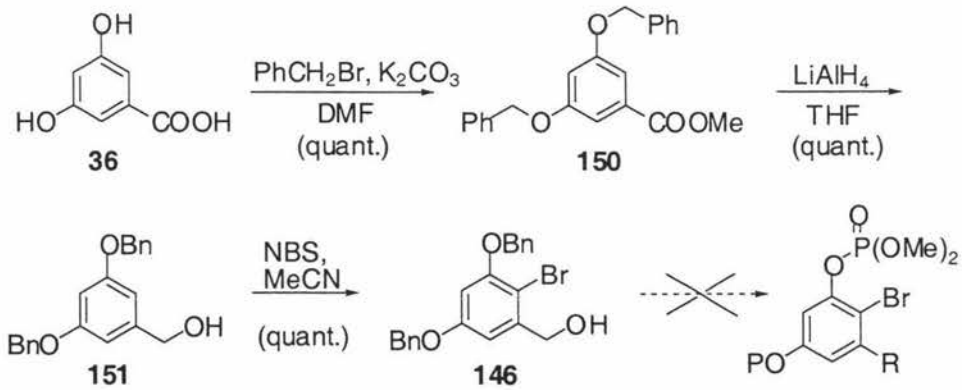
Attempted hydrogenolysis to remove the benzyl ethers from compound **155** was accompanied by cleavage of the acetate. Retrospectively, this is not surprising since the acetate ester is also benzylic. Selective cleavage of the two unsubstituted benzyl ethers (protecting groups) is actually unlikely to be achieved in the presence of esters/ethers of the "core" aromatic benzyl alcohol. Thus, the alcohol oxidation state is not compatible with the use of benzyl ether protecting groups.

We therefore reverted to the acid oxidation state, employing methyl ester **150**. Bromination with NBS was successful (Scheme 3.34) to give compound **156**, and removal of the benzyl groups was attempted by hydrogenolysis. The benzyl groups were successfully removed, but hydrodehalogenation of the aryl bromide had also occurred. This wasn't anticipated but turned out to be a well known reaction.[20]



Scheme 3.34

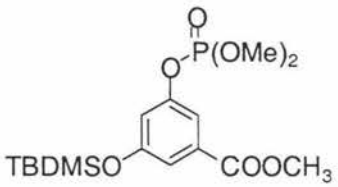
In summary, although we never arrived at the rearrangement substrate, regioselective bromination of the aromatic ring was successfully achieved. While several quantitative steps made this approach potentially efficient (Scheme 3.35), the removal of benzyl ethers by hydrogenation is incompatible with the bromo-substituent which is key in our plan for metal-halogen exchange. Hydrogenation is also incompatible with the alcohol oxidation state, since it is not possible to distinguish between the protecting groups and the "core" aromatic ring.



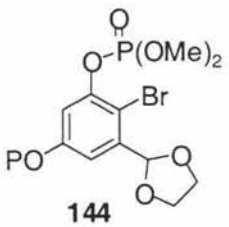
Scheme 3.35

3.3 Route C: Protection of Phenols as *para*-Methoxybenzyl Ethers

The failure of Routes A and B was attributable in both cases to the protecting groups of the phenol and their unanticipated incompatibility with the reaction chemistry. In route A, the TBDMS group was found to be unstable in the presence of a phenolate anion, causing problems in base-promoted protection and phosphorylation, as well as in the rearrangement of compound **117** itself. Route B adopted the benzyl ether as the temporary phenol protecting group. Unfortunately, hydrogenolysis of these ethers was accompanied by reductive cleavage of the Ar-Br bond and benzylic acetal functional groups in compounds such as **144** and **146**.



117



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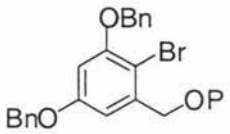
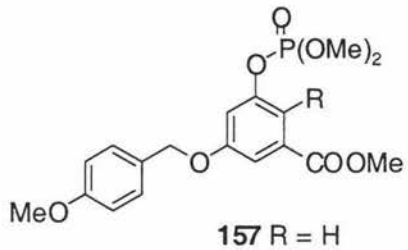


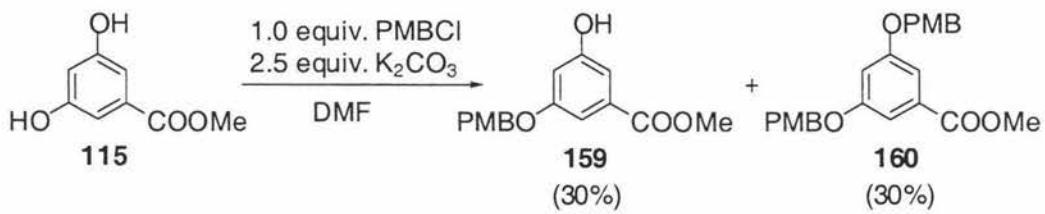
146 (P = H)

Hence, a third route was developed to incorporate a new phenol protecting group that would be stable to phenolate anions and could be removed without using hydrogenolysis. The protecting group chosen was the *p*-methoxybenzyl (PMB) ether and thus our ultimate target was compound **158**. We hoped the PMB group would provide the steric hinderance required in the rearrangement to give the desired regioselectivity. Another important feature of the PMB ether is the mild oxidative reaction conditions available for its removal.[21]



157 R = H
158 R = Br

Protection of one of the phenols was attempted using the conditions similar to those employed in Route B for the formation of the two benzyl ethers. This approach yielded a mixture of the di- and mono-protected products along with recovered starting material (Scheme 3.36). Attempts to improve this reaction by creating the mono-phenolate anion with NaH prior to the addition of the alkylating agent were unsuccessful. We also tried to generate a better leaving group *in situ,* by including tetrabutyl ammonium iodide in the reaction mixture. This gave the same distribution of **115**, **159** and **160**.



Scheme 3.36

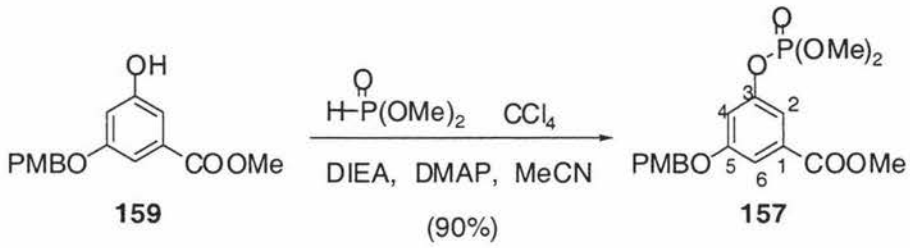
The incorporation of the PMB group in compound **159** was confirmed by the appearance of two doublets of doublets at δ 6.90 and 7.33 ppm in the aromatic region of the ^{1}H NMR spectrum and a singlet at δ 4.96 ppm due to the benzylic protons. A characteristic singlet due to the methoxy group was also seen at δ 3.80. Due to the decrease in the symmetry of

the molecule (relative to the starting material), the aromatic region featured three distinct signals due to the three protons of the "core" aromatic ring.

The spectrum of the *bis*-protected product showed only two aromatic signals in a 2:1 ratio, since this molecule is symmetrical. Integration of the signals attributed to the PMB group confirmed the presence of two such protecting groups.

As experienced in Route A, introducing a single phenol protecting group was problematic, but the formation of the *bis*-protected compound is easily achieved. A series of oxidative removals were investigated as a means of selectively removing one PMB group from compound **160**. If successful, this would have offered a solution to the low yielding mono-protection reaction. This was first attempted using CAN (ceric ammonium nitrate) using a published procedure.[21] *p*-Methoxybenzaldehyde was isolated from this reaction, indicating that the PMB groups had been detatched from the "core" aromatic ring. However, no product **159** was isolated or even seen by TLC. Two other reagents were investigated: DDQ[21] and $CeCl_3.7H_2O$ with NaI.[22] These reactions yielded multiple products, but not resulting from the desired removal of one PMB ether.

Phosphorylation of the remaining free phenol in compound **159** was achieved using the Atherton-Todd conditions, described earlier (Scheme 3.37).

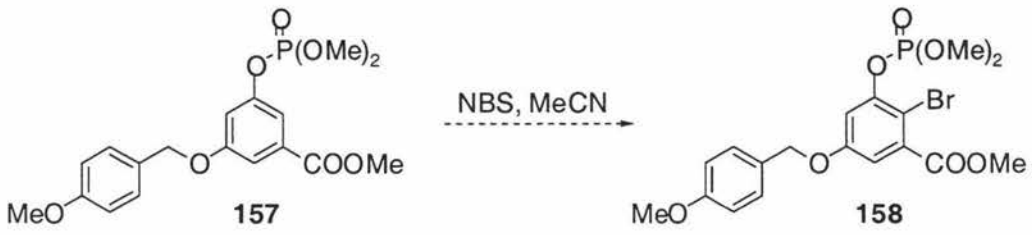


Scheme 3.37

The two methyl phosphate esters in compound **157** are chemically equivalent. However, the protons of these methyl groups will exhibit a ^{3}J coupling to the phosphorus, resulting in a doublet. The appearance of a doublet at δ 3.8 in the ^{1}H NMR spectrum, and a doublet at δ 55.0 ppm (J = 6 Hz) in the ^{13}C NMR spectrum confirmed the presence of the phosphate ester. This was reinforced by the splitting of the nearby signals: C2 (^{3}J = 5 Hz), C3 (^{2}J = 7 Hz) and C4 (^{3}J = 5 Hz) in the ^{13}C NMR spectrum.

While compound **157** could serve as a substrate for the anionic phospho-Fries rearrangement, we sought to remove all doubt about the regioselectivity of the rearrangement by invoking metal-halogen exchange to generate the anion. Introduction of the requisite Br into the desired position was well precedented in Route B.

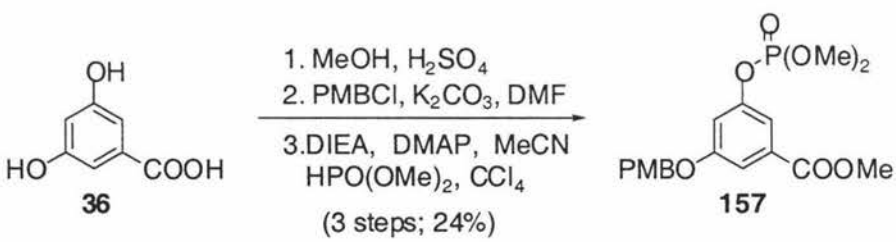
We therefore attempted mono bromination of compound **157** utilizing NBS. Unfortunately, the bromination could not discriminate between the "core' aromatic ring and that of the PMB group, giving a mixture of different brominated products that were difficult to separate. This occurs because both aromatic rings are electron-rich, *c.f.*, in Route B where there is a significant differential in electron density between the "core" and "protecting group" aromatic rings.



Scheme 3.38

While the bromination was unsuccessful, we anticipated that the steric hindrance of the PMB group, combined with the enhanced acidity of the proton between the phosphate and the methyl ester, would be sufficient in directing the rearrangement. We hoped that the bromine was a luxury we could proceed without.

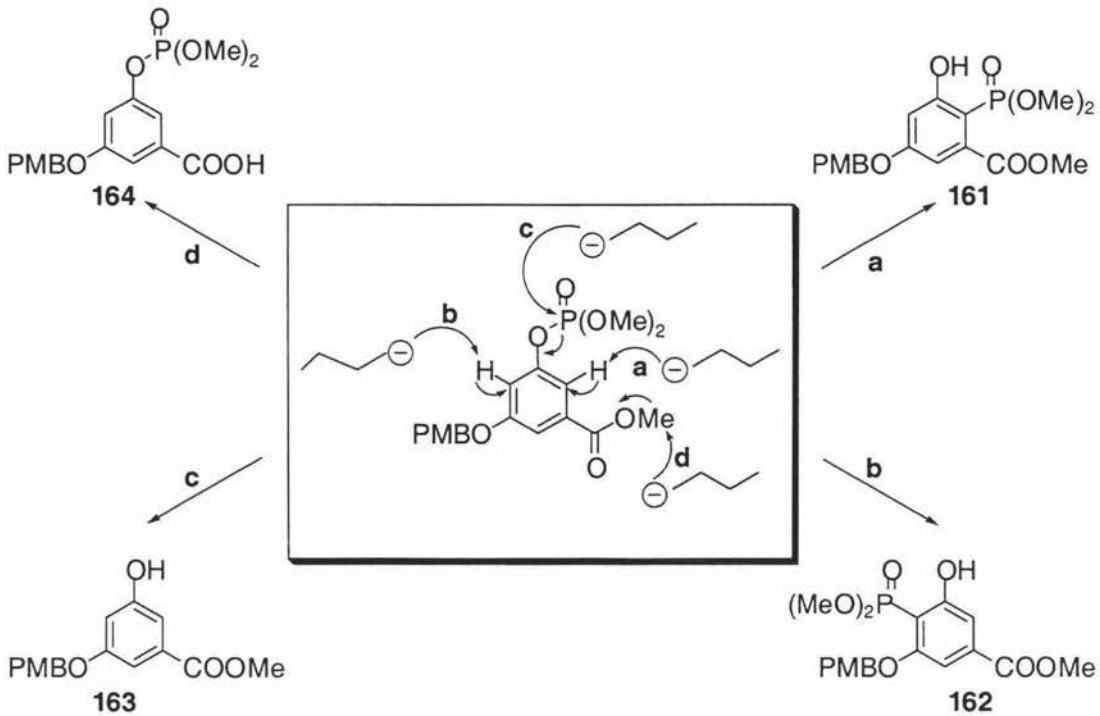
In summary, we produced our third substrate in three steps in an overall yield of 24% (Scheme 3.39). Once again, the monoprotection step was the stumbling block, proceeding in only 30% yield. However, the overall preparation of **157** was short and relatively efficient.



Scheme 3.39

The anionic phospho-Fries rearrangement of substrate **157** was then examined. As seen earlier, attempted rearrangement with *n*-BuLi at –78 °C led to a complex mixture of products depicted in Scheme 3.40. Compounds **163** and **164** resulted from nucleophilic

attack at the phosphate and the carboxylate esters respectively. The rearranged product was isolated in low yield.

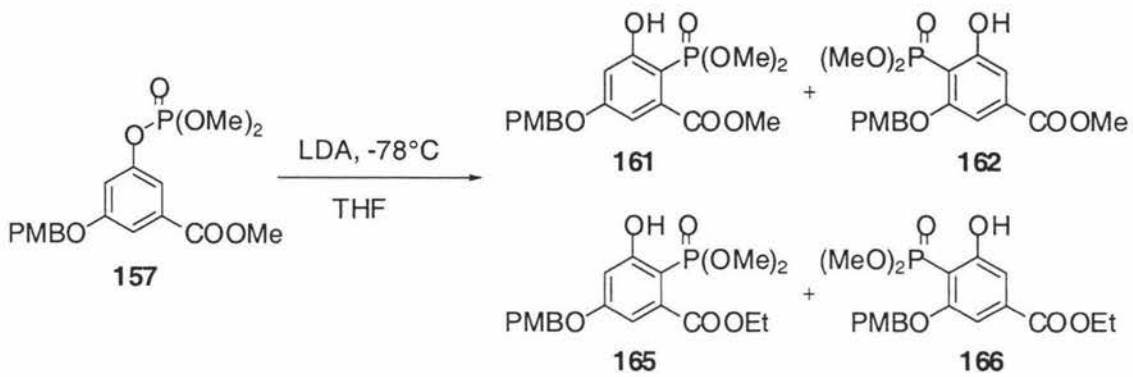


Scheme 3.40

There are two features of the NMR spectra that provide strong evidence for the rearrangement. The direct C-P bond has a large coupling constant (~180 Hz), and hence gives rise to a distinct doublet in the ^{13}C NMR spectrum. Secondly, the phenolic proton is strongly hydrogen bonded to the phosphoryl oxygen, resulting in a downfield shift (10-12 ppm).

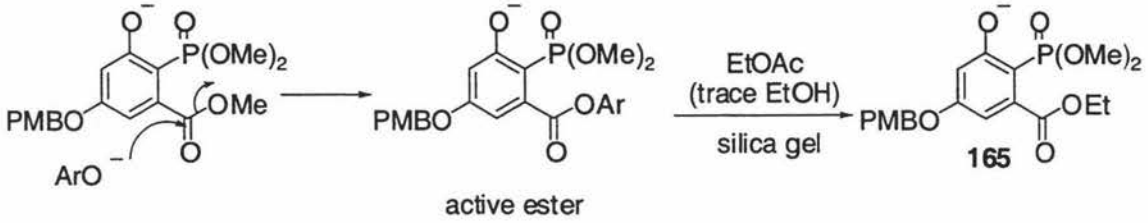
Lithium diisopropylamide was then employed in place of *n*-BuLi, since the steric bulk of this base has previously been reported to eliminate the formation of the undesired products

arising from nucleophilic behaviour. The LDA was generated *in situ* following a published procedure, using N,N-diisopropylamine and *n*-BuLi in a 1.3:1.5 ratio. The product mixture of this reaction contained more than the two anticipated regioisomeric products. The ^{1}H NMR spectrum of the mixture strongly suggested the presence of an ethyl ester, with a quartet at δ 4.37 and a triplet at δ 1.35 in a ratio of 2:3. Indeed, 2D NMR spectra, HPLC analysis, and mass spectrometry of the product mixture confirmed that transesterification of the methyl ester had occurred. The HPLC trace (Figure 3.3.2) showed four peaks, corresponding to the four compounds depicted in Scheme 3.41.



Scheme 3.41

We propose that transesterification occurs via an aryl ester arising from displacement of the methyl ester by the nucleophilic phenolate anion. While we had not previously seen this, we have experienced the phenolate anion's nucleophilicity. The active ester reacts during silica gel column chromatography with trace ethanol in the eluent.



Scheme 3.42

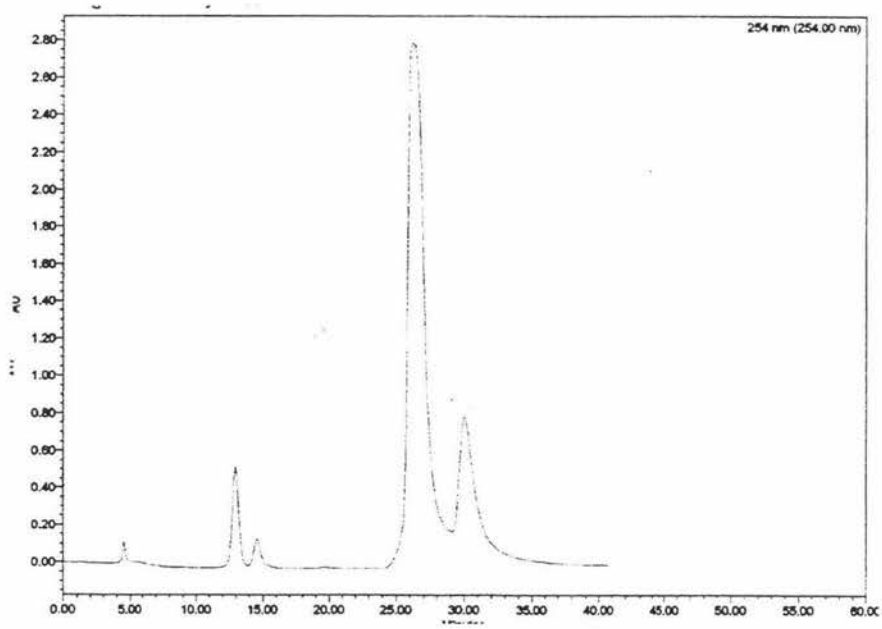
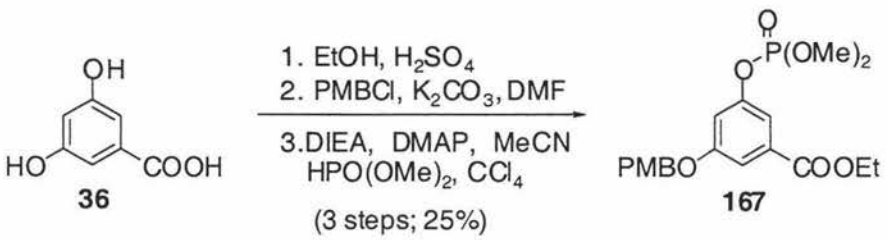


Figure 3.2 HPLC Chromatogram of product mixture.

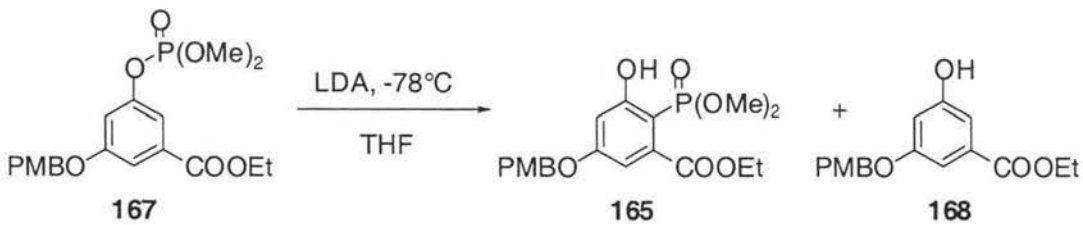
The major product, corresponding to the third peak was isolated by normal phase HPLC, characterized by NMR and mass spectrometry, and shown to be the ethyl ester.

To avoid this transesterification problem, the analogous substrate was synthesized *de novo* with an ethyl ester in place. All steps gave the expected results with parallel yields.



Scheme 3.43

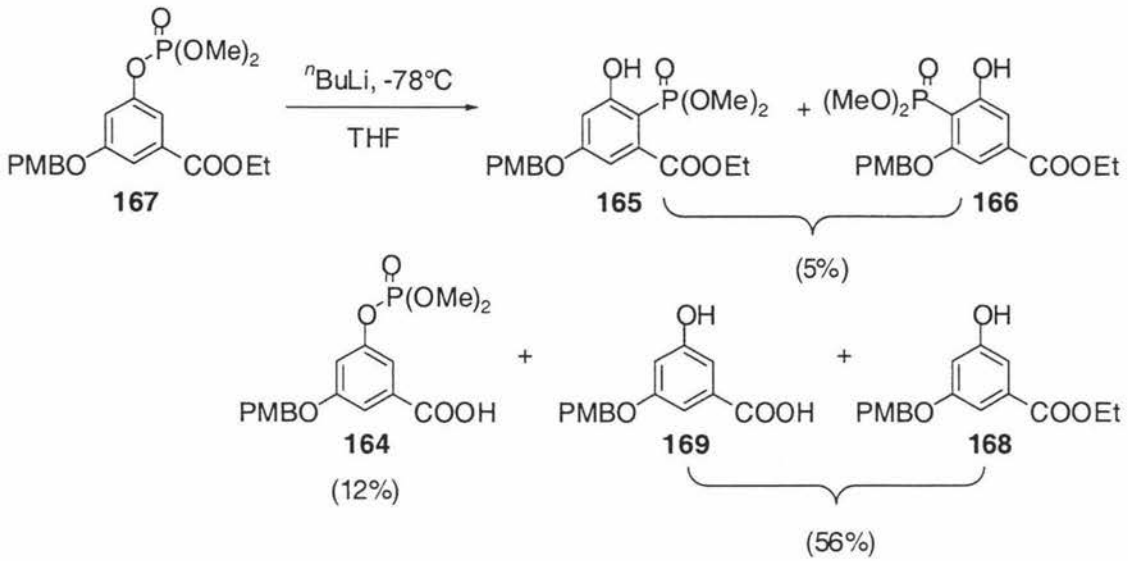
As had been done previously, rearrangement of this substrate was induced by generating LDA *in situ* from diisopropylamine and *n*-BuLi in a 1.3:1.5 ratio. The reaction yielded 40% of the rearranged product as a mixture of both regioisomers, along with compound **168** resulting from nucleophilic attack at the phosphorus. Not all of the starting material was consumed during the reaction.



Scheme 3.44

We hypothesised that the formation of compound **168** was due to the presence of excess *n*-BuLi. Since our supply of this reagent had deteriorated, a new bottle was opened and titrated to establish the concentration accurately. The rearrangement was then repeated using what we hoped was an accurate 1:1 ratio of *n*-BuLi/DIA. This time only a 25% yield of the desired rearranged product was isolated, along with an approximately 50% yield of undesired products that seemed to have suffered nucleophilic attack at both ester

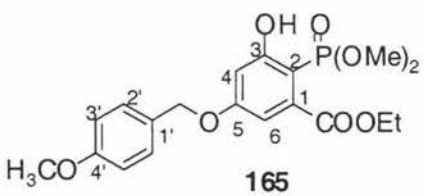
functionalities. The reaction was repeated with *n*-BuLi (not LDA) to more thoroughly investigate this behaviour. The reaction yielded a complex mixture of products. The bulk of the reaction products (56%) appeared to be a mixture of two products, both a result of *n*-BuLi behaving as a nucleophile. The two regioisomers (*i.e.*, products **165** and **166**) were obtained in low yield and were inseparable by flash column chromatography. The ^{1}H NMR spectrum indicated a 1 : 1.3 ratio of the two isomers.



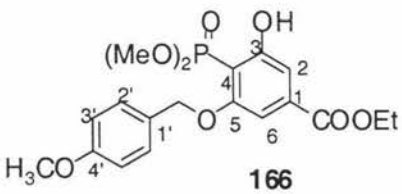
Scheme 3.45

The rearrangement was then attempted using a 1:1 ratio of *n*-BuLi and (*i*-Pr$_2$)NH to eliminate the presence of any excess *n*-BuLi. The reaction gave 64% of a mixture of regioisomers, along with small amounts of products encountered previously. The ^{1}H NMR indicated that the isomers occurred in a 1:6 ratio. This was confirmed by HPLC analysis with peak 2 isolated and established to be a single isomer by ^{1}H NMR.

The reaction conditions were modified further to minimize the formation of products arising from the base behaving as a nucleophile. The rearrangement reactions to-date had been allowed to warm to room temperature, according to literature procedures. As starting material was still evident at termination, we allowed the reaction to stir for longer at room temperature. This produced a higher ratio of undesired products. It was found that if the reaction was quenched after the hour at –78 °C without warming to room temperature, higher yields of rearranged product occurred (*i.e.*, 76%) with only small amounts of unreacted starting material being recovered. Longer reaction times at –78 °C saw the reaction go to completion eventually and this was accompanied by greatly improved regioselectivity. Characterization of the rearranged product showed almost 100% of a single regioisomer. This led us to thoroughly characterize the product, to confirm which regioisomer it was.



165



166

The ^{1}H NMR signals could be assigned to the various functional groups, but the 1D data were consistent with both isomers. The COSY spectrum showed a correlation between the more downfield aromatic PMB signal and the benzylic protons, allowed a distinction to be made between H2' and H3' aromatic signals.

Table 3.3 ^{1}H NMR Data for Rearranged Product

δ (multiplicity)	Assignment
1.39 (t)	$CH_2C\mathbf{H}_3$
3.69 (d)	$P(OC\mathbf{H}_3)_2$
3.82 (s)	$OC\mathbf{H}_3$
4.38 (q)	$C\mathbf{H}_2CH_3$
5.10 (s)	$C\mathbf{H}_2Ar$
6.92 (d)	H2'
7.03 (d)	H2/H4/H6
7.11 (d)	H2/H4/H6
7.37 (d)	H3'
11.32 (s)	O**H**

The ^{13}C NMR (0-150 ppm region) was assigned with the help of the 135° DEPT and HMQC spectra. As expected, the ^{13}C signal attributable to the phosphate methyl esters was split with a coupling constant of 5.4 Hz. The signals corresponding to the carbons *meta* to the phosphorus substituent were split, with three-bond coupling constants of 12.3 and 8.4 Hz.

Table 3.4 ^{13}C NMR Data for Rearranged Product (0-150 ppm)

δ (multiplicity)	Assignment	δ (multiplicity)	Assignment
13.9	$COOCH_2\mathbf{C}H_3$	102.4 (d)	**C**-CP
53.3 (d)	$P(O\mathbf{C}H_3)_2$	111.7 (d)	**C**-CP
55.1	$ArO\mathbf{C}H_3$	113.7	C2' or C3'
61.4	$COO\mathbf{C}H_2CH_3$	127.8	C1'
70.4	$\mathbf{C}H_2Ar$	128.9	C2' or C3'
100.3 (d)	**C**-P	137.1	**C1**

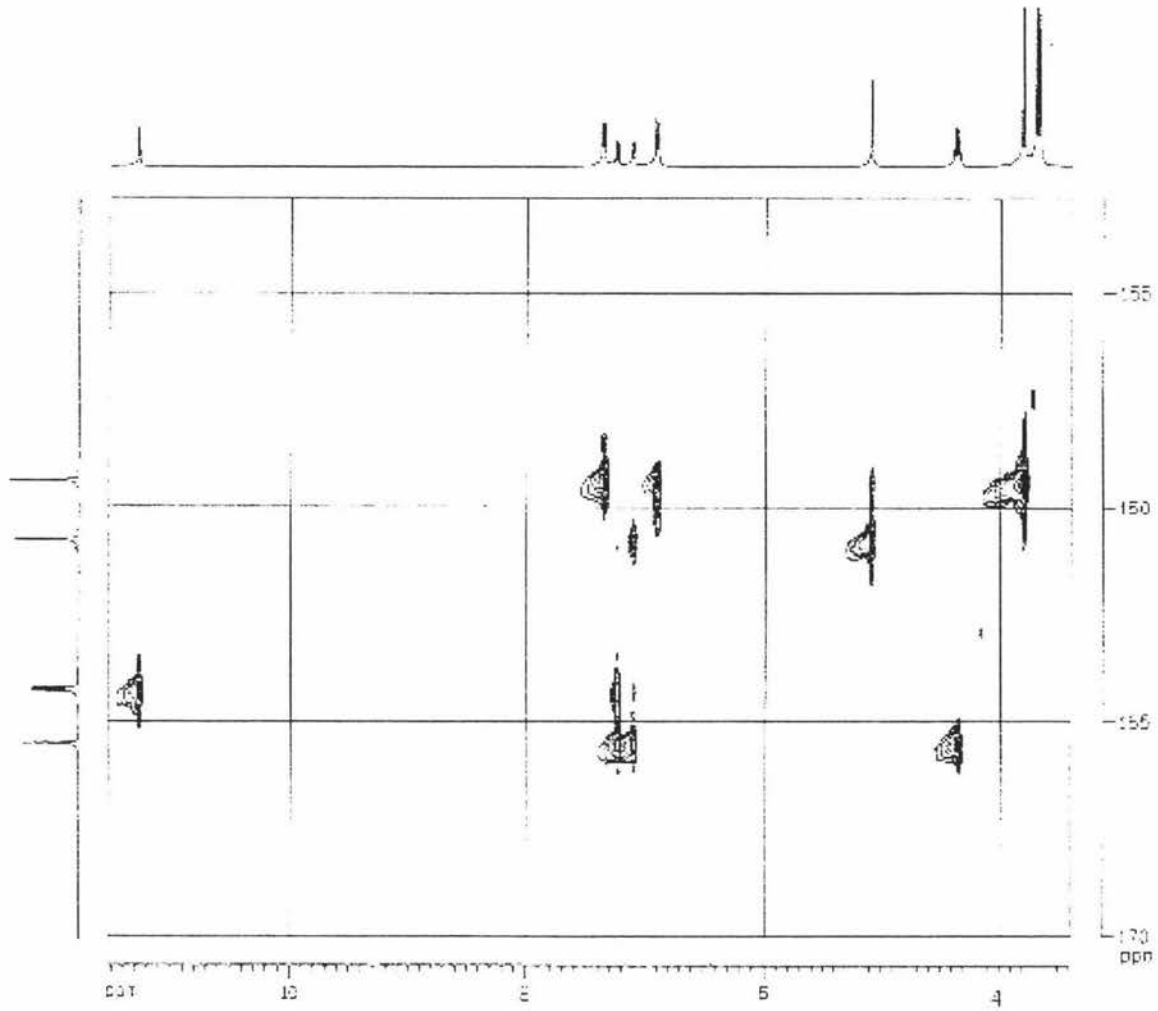


Figure 3.4 HMBC Spectrum.

The downfield region (158-166 ppm) of the ^{13}C NMR spectrum contained the four peaks, attributable to C3, C5, COOEt and C4'. The signal at 164 ppm is split (J = 5.4 Hz) indicating that this carbon is adjacent to the phosphorus, and can therefore be assigned as C2 of **165** or C4 of **166**. This does not help distinguish between the two regioisomers. The HMBC spectrum was helpful in assigning these signals. The signal at δ 159 was readily assigned to C4', due to its correlations with both aromatic PMB signals (the doublets at 6.92 and 7.37 ppm) and the characteristic CH_3O singlet. The COOEt carbon should show a

correlation to the protons of the ethyl ester group ($COOCH_2CH_3$); the only signal to do so was the signal at δ 165. This ^{13}C signal also showed correlations to both "core" aromatic proton signals. This indicated rearrangement to position 4 had occurred. Assignment of the remainder of this region agreed with this conclusion, with C5 being assigned on the basis of its correlation to the benzylic protons, showing only one correlation to the "core" aromatic signals (*c.f.*, two expected if the desired regioisomer). Also, the signal due to C3 of structure **166** showed crosspeaks with the phenol (*i.e.*, proton at 11.32 ppm), and one of the "core" aromatic signals (H2, δ).

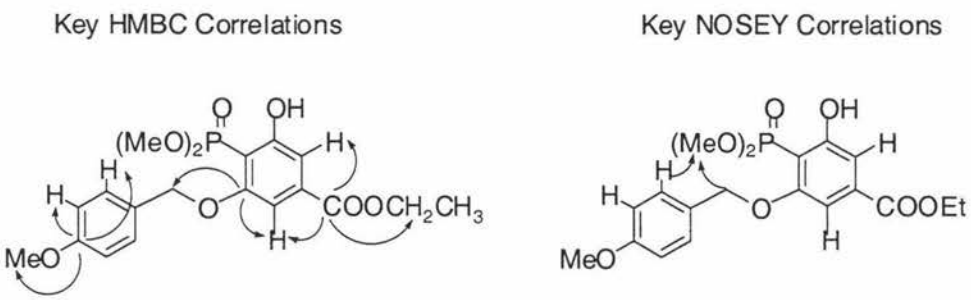


Figure 3.5 2D correlations

The NOESY spectrum confirmed this assignment. In the desired isomer, **165**, protons of the phosphate ester and ethyl ester are close in space and therefore might be expected to give rise to a crosspeak in the NOESY spectrum. There was no trace of this. Instead, a weak correlation between the phosphate esters and one of the aromatic PMB signals indicated that these groups were in close proximity, confirming that rearrangement to the position 4 had occurred.

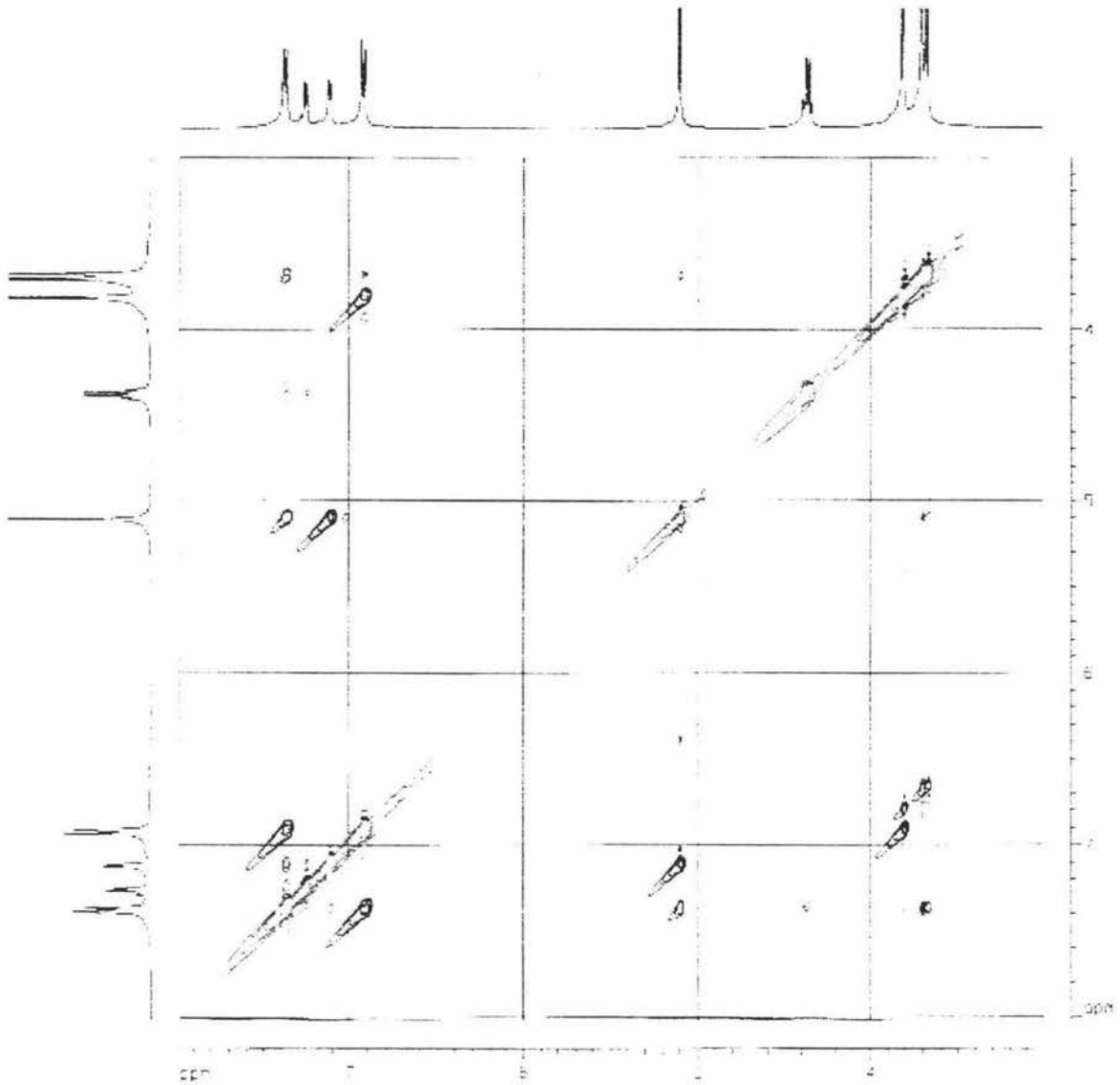


Figure 3.6 NOESY spectrum

As seen in previous examples, coordination of methyl ethers to Li occurs. We propose that the PMB group has the same coordinating ability, directing the rearrangement between the phosphate and PMB group. We had hoped that the PMB group would be bulky enough to direct metalation away from itself.

3.4 Future Work

The remaining obstacle in the synthesis of the aromatic fragment **29**, is the issue of regioselectivity in the anionic phospho-Fries rearrangement. There are two possible means of eliminating this problem.

1) Incorporate a phenol protecting group with enough steric hindrance to direct metalation to position 2.
2) Introduce bromine to position 2 of the aromatic ring, invoking metal-halogen exchange.

It has been shown that the regioselectivity of an anionic phospho-Fries rearrangement can be controlled by the steric effects of substituents of the aromatic ring. There are several phenol protecting group options available, but there is always the possibility of the formation of both regioisomers, which are difficult to separate. The introduction of a bromine to the aromatic ring, provides a more secure means of gaining the required regioselectivity.

Mono-bromination of an aromatic ring is a long standing problem. There is precedent for tetrabutylammonium tribromide and derivatives as a reagent to do this. Our attempts with this reagent have proven unsuccessful, but we feel this has to be attributable to poor quality reagent. There is thus still a possibility for the use of such a reagent in the bromination of the aromatic fragment. The introduction of a bromine using NBS required the phenols to be protected, which means a longer synthetic sequence and ultimately a less efficient production of the hapten (**26**).

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4. EXPERIMENTAL PROCEDURES

General Experimental Methods

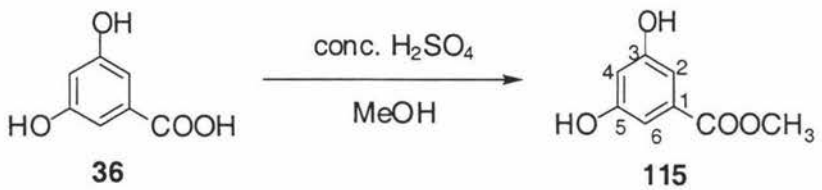
Reactions were carried out under an atmosphere of nitrogen. Tetrahydrofuran was freshly distilled from sodium/benzophenone. Dichloromethane was freshly distilled from calcium hydride. Pyridine, triethylamine and N,N-diisopropylethylamine were dried and distilled from CaH_2 and stored over KOH pellets. DMF was dried and distilled from BaO and stored over molecular sieves. *t*-Butyldiphenylsilylchloride, diethylphosphite, 2.5 M *n*-BuLi in hexane and tetrabutylammonium iodide were obtained from Acros. Imidazole, 10% Pd/C, and potassium carbonate were obtained from BDH. Bromine and sodium iodide were obtained from Hopkin and Williams. Benzyl bromide, lithium aluminium hydride, oxalyl chloride, 1.6 M *n*-BuLi in hexane, N,N-dimethylaminopyridine, N,N-diisopropylamine and *t*-butyldimethylsilyl chloride from Merck. Tetrabutylammonium tribromide was obtained from Alfa Aesar. Sodium hydride and *N*-bromosuccinimide were obtained from Riedel-de-Haen. *t*-Butylammonium fluoride was from Avocado. Dimethylphosphite was from Lancaster. *p*-Methoxybenzylchloride and sodium methoxide were obtained from Aldrich. Cresol was obtained from Sigma. Acetic anhydride was from Ajax Chemicals.

Reactions were followed by TLC on Merck 0.25 mm silica gel 60 F_{254} on aluminium backed sheets, visualized under a UV lamp. Flash column chromatography was carried out

according to Still *et al.*[1] using Scharlau silica gel 60, 0.04-0.06 mm, 230-400 mesh. HPLC was performed on a Waters 600E HPLC system equipped with a Waters 2487 UV detector (254 nm).

NMR spectra were recorded on a JEOL JNM-GX270W spectrometer. Proton spectra were recorded at 270 MHz and referenced relative to the residual solvent signal, $CDCl_3$ (7.27 ppm) or CD_3OD (3.30 ppm). Carbon NMR spectra were recorded at 67.5 MHz and are reported in ppm relative to solvent as internal standard. 2D NMR spectra wee recorded ona Bruker Avance 400 spectrometer. Mass spectra were recorded on a VG70-250S mass spectrometer, using FAB ionization with a NBA/CH_2Cl_2 matrix.

Methyl 3,5-dihydroxybenzoate (115)[1]

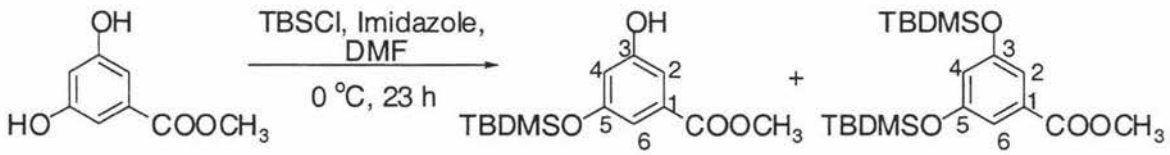


36 **115**

A solution of α-resorcyclic acid (**36**) (1.003 g, 6.51mmol) in methanol (9 mL) was treated with concentrated sulfuric acid (0.1 mL) and heated at reflux for 5 h with the reaction being followed by TLC. After 5 h the methanol was removed *in vacuo* and the residue taken up in ethyl acetate (50 mL). The resulting solution was then washed successively with sat'd aq. $NaHCO_3$ (25 mL), water (25 mL) and brine (25 mL). The ethyl acetate solution was then dried over $MgSO_4$, filtered and concentrated to yield the methyl ester (**115**) as a colourless

solid (0.997 g, 91%). m.p.169-172 °C (*Lit. ref* 168-170 °C). R_f 0.24 (95:5 CH_2Cl_2/MeOH). ^1H NMR (CD_3OD, 270 MHz) δ 3.85 (s, 3H $COOCH_3$), 6.46 (t, *J*= 2.4 Hz, 1H, H4), 6.92 (d, *J*= 2.4 Hz, 2H, H2, H6). ^{13}C NMR (CD_3OD, 270 MHz) δ 52.5 ($COOCH_3$), 108.1 (C4), 108.7 (C2, C6), 132.8 (C1), 159.4 (C3, C5), 168.5 ($COOCH_3$). LRMS (EI^+) M^+ 168.

Methyl 5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-hydroxybenzoate(116)[2]

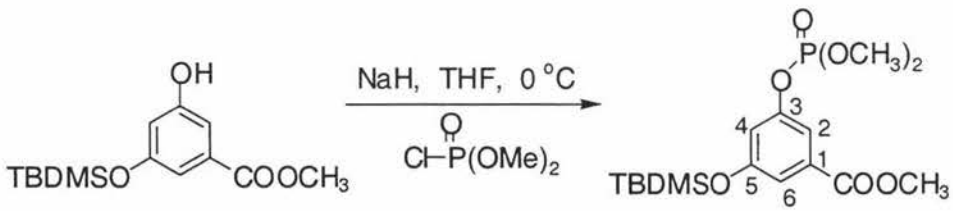


115 **116** **120**

A solution of imidazole (0.2431 g, 3.57mmol, 1.2 equiv.) and *tert*-butyldimethylsilyl chloride (0.4935 g, 3.27 mmol, 1.1 equiv.) in DMF (5 mL) was added dropwise to a solution of methyl 3,5-dihydroxybenzoate (**115**) (0.5009 g, 2.98 mmol, 1.0 equiv.) in DMF (5 mL) at 0 °C. The solution was warmed to room temperature and stirred for 23 h under an atmosphere of nitrogen. The solution was diluted with ethyl acetate (25 mL) and washed with water (25 mL). The aqueous layer was then re-extracted with ethyl acetate (25 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with 5:1 hexane/ethyl acetate afforded the disilylated compound (**120**), (0.2699 g, 23 %). R_f 0.74 (3:1 Hex/EtOAc). ^1H NMR ($CDCl_3$, 270 MHz) δ 0.20 (s, 12H, $Si(CH_3)_2$), 0.96 (s, 18H, $SiC(CH_3)_3$), 3.86 (s, 3H, $COOCH_3$), 6.50 (t, *J* = 2.4 Hz, 1H, H4), 7.11(d, *J* = 0.66 Hz, 2H, H2, H6); ^{13}C NMR ($CDCl_3$, 270 MHz) δ -4.5 ($Si(CH_3)_2$), 18.3

($SiC(CH_3)_2$), 22.8 ($SiC(CH_3)_3$), 52.2 ($COOCH_3$), 114.5 (C2, C6), 116.7 (C4), 131.7 (C1), 156.4 (C3, C5), 166.6 ($COOCH_3$); LRMS (EI^+) M^+ 396. Further elution gave the desired monosilyl compound (**116**) (0.44 g, 52%), as a colourless oil. Compound **116** was recrystallised from hexane to yield a colourless solid. m.p. 76-83 °C (*Ref lit* 77-78.5 °C). R_f 0.37 (3:1 Hex/EtOAc). ^1H NMR ($CDCl_3$, 270, MHz) δ 0.20 (s, 6H, $Si(CH_3)_2$), 0.98 (s, 9H, $SiC(CH_3)_3$), 3.90 (s, 3H, $COOCH_3$), 6.25 (s, 1H, OH), 6.58 (t, J = 2.3 Hz, 1H, H4), 7.07 (dd, J = 1.3 Hz, 1H), 7.21 (dd, J = 1.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 270 MHz) δ -4.4 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$) 52.3 ($COOCH_3$), 109.6 (C4), 112.2 (C6), 113.7 (C2), 131.7 (C1), 156.5 (C3), 156.7 (C5), 166.9 (COOMe). LRMS (EI^+) M^+ 282. The elutant was changed to 9:1 dichloromethane/methanol and starting material (**5**) was recovered (0.1867 g, 37%).

Methyl 3 - dimethylphosphato- 5 -[[(1,1-dimethylethyl)dimethylsilyl]oxy]benzoate (117)

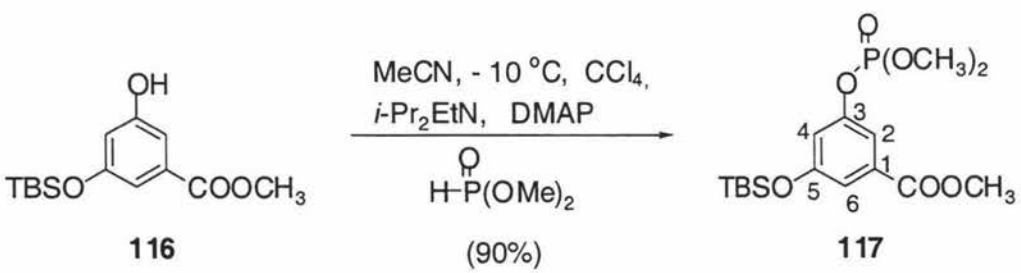


116 **117**

Sodium hydride (0.0187 g, 0.780 mmol, 1.1 equiv., 60% oil dispersion) was added to a solution of phenol **116** (0.2013 g, 0.709 mmol, 1 equiv.) in THF (6 mL) under an atmosphere of nitrogen. After H_2 evolution ceased, the soluton was cooled to 0 °C and

stirred for 5 min. A solution of dimethylchlorophosphate (0.1023 g, 0.709 mmol, 1 equiv.) in THF (2 mL) was added dropwise and the solution was stirred for 2 h under an atmosphere of nitrogen at 0 °C. The solvent was removed by evaporation to give the crude product mixture. The products were isolated by flash chromatography, eluting with 5:1 hexane/ethyl acetate to give the disilyated compound **7** (64.4 mg, 23%), recovered startng material **116** (20.0 mg, 10%), and the desired compound **117** (106.7 mg, 39%) as a colourless oil. R_f 0.13 (3:1 Hex/EtOAc). ^{1}H NMR ($CDCl_3$, 270 MHz) d 0.21 (s, 6H, $Si(C\mathbf{H}_3)_2$), 0.96 (s, 9H, $SiC(C\mathbf{H}_3)_2$), 3.83 (s, 3H, $COOC\mathbf{H}_3$), 3.88 (d, J = 1.75 Hz, 6H, $P(OC\mathbf{H}_3)_2$), 6.91 (m, 1H), 7.31 (m, 1H), 7.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 270 MHz) d -4.5 ($Si(\mathbf{C}H_3)$, 18.2 ($Si\mathbf{C}(CH_3)$), 25.6 ($SiC(\mathbf{C}H_3)$), 52.3 ($COO\mathbf{C}H_3$), 54.9 (d, J = 6 Hz, $P(O\mathbf{C}H_3)_2$), 113.8 (d, J = 5 Hz, C2), 116.5 (d, J = 5 Hz, C4), 117.9 (C6), 132.2 (C1), 150.9 (d, J = 7 Hz, C3), 156.5 (C5), 165.7 ($\mathbf{C}OOCH_3$); LRMS (EI^+) M^+ 390. The elutant was changed to 95:5 dichloromethane/methanol to give the methyl ester **5** (42.4 mg, 27%).

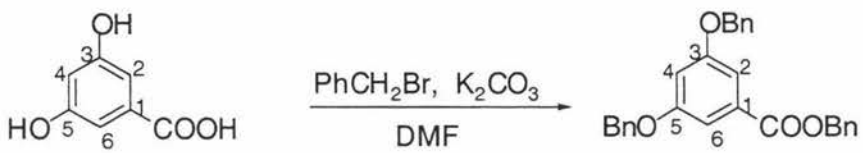
Methyl 3 – dimethylphosphato – 5 - [[(1,1-dimethylethyl)dimethylsilyl]oxy]benzoate via Atherton-Todd conditions



116 (90%) **117**

Carbon tetrachloride (0.6838 mL, 7.08 mmol, 5.0 equiv.) was added to a solution of phenol **6** (0.4001 g, 1.42 mmol, 1 equiv.) in MeCN (10 mL) at -10^{0} C and stirred for 5 min under an atmosphere of nitrogen. Diisopropylethylamine (0.3848 g, 2.98 mmol, 2.1 equiv.) and DMAP (0.0173 g, 0.14 mmol, 0.1 equiv.) were added and the solution stirred for a further 1 min. Dimethylphosphite (0.1884 mL, 2.06 mmol, 1.45 equiv.) was then added dropwise maintaining a temperature of $< -10^{0}$ C and left to stir for approximately 45 min. The reaction was then quenched with 0.5 M aq. KH_2PO_4 (3 mL) and allowed to warm to room temperature. The solution was diluted with ethyl acetate (50 mL), washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the phosphorylated compound **8** (0.493 g, 89%) as a colourless oil. Data as above.

Benzyl 3,5-*bis*(Benzoxy)benzoate (149)[3]

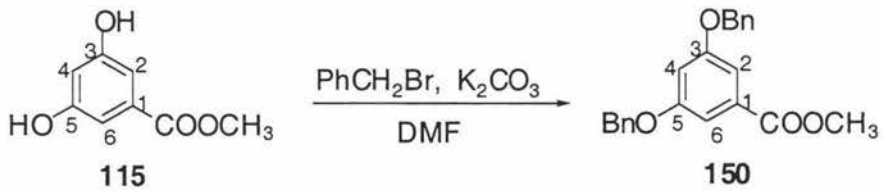


36 **149**

Benzyl bromide (3.625 mL, 5.214 g, 30 mmol, 3.7 equiv.) was added dropwise to a solution of α-resorcylic acid (**36**) (1.467 g, 9.53 mmol, 1.0 equiv.) and K_2CO_3 (6.58 g, 47 mmol, 5.0 equiv.) in DMF (15 mL) under an atmosphere of nitrogen. This was stirred at room temperature for 1 h. More benzyl bromide (570 μL, 810 mg, 4.76 mmol, 0.5 equiv.) was added and the solution stirred for a further 3 h. The reaction mixture was diluted with ethyl aetate (75 mL), washed with water (2 x 75 mL) and brine (80 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a quantitative yield of compound **149** as a

colourless solid. R_f 0.50 (3:1 Hex/EtOAc). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.10 (s, 4H, OC**H**$_2$Ar) 5.39 (s, 2H, H2, H6), 6.85 (m, 1H, H4), 7.30-7.50 (m, 10H, Ar-H).

Methyl 3,5-*bis*(Benzoxy)benzoate (150)[4]

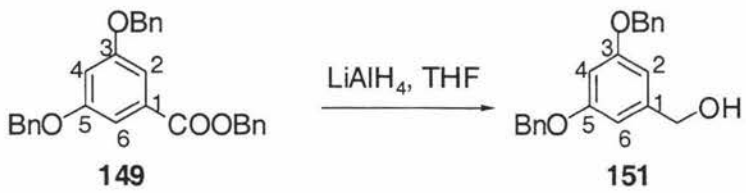


115 **150**

Benzyl bromide (0.88 mL, 1.3251 g, 7.440 mmol, 2.5 equiv.) was added dropwise to a solution of ester **115** (0.5009 g, 2.976 mmol, 1.0 equiv.) and K_2CO_3 (2.0567 g, 14.9 mmol, 5.0 equiv.) in DMF (5 mL) under an atmosphere of nitrogen. This was stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a quantitative yield of compound **150** as a colourless solid. Data was in good agreement with the literature. R_f 0.69 (1:1 Hex/EtOAc). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.91 (s, 3H, COOC**H**$_3$), 5.07 (s, 4H, OC**H**$_2$Ph), 6.81 (t, J = 2.4 Hz, 1H, H4), 7.30 (d, J = 2.4 Hz, 2H, H2 and H6), 7.33-7.45 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 52.3 (COO**C**H$_3$), 70.3 (O**C**H$_2$Ph), 107.2 (C4), 108.3 (C2, C6), 127.5 128.0 128.5 (Ph), 131.9 (C1), 136.4 (Ph), 159.6 (C3, C5), 166.6 (**C**OOCH$_3$).

3,5-*bis*-(Benzoxy)benzyl alcohol[4b,5]

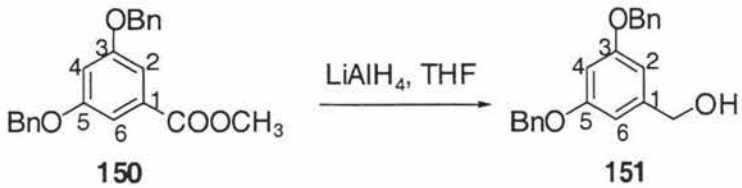
(a) From compound 149



149 **151**

A solution of **149** (1.903 g, 4.48 mmol, 1.0 equiv.) in THF (10 mL) was added slowly to a stirred suspension of $LiAlH_4$ (255.5 mg, 6.73 mmol, 1.5 equiv.) in THF (10 mL) under an atmosphere of nitrogen. The mixture was stirred at room temperature for 2 h before another portion of $LiAlH_4$ (119.0 mg, 3.14 mmol. 0.7 equiv) was added. After 15 min the reaction was quenched with methanol (10 mL) and stirred for a further 10 min. The mixture was then diluted with ethyl acetate (50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography of the residue with 5:1 hexanes/ethyl acetate gave compound **151** (984.0 mg, 68%) as a colourless solid. R_f 0.58 (1:1 Hex/EtOAc). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.10 (s, 1H, $CH_2O\mathbf{H}$), 4.61 (s, 2H, $ArC\mathbf{H}_2OH$), 5.03 (s, 4H, $OC\mathbf{H}_2Ph$), 6.56 (t, J = 2.2 Hz, 1H, H4), 6.63 (d, J = 2.2 Hz, 2H, H2 and H6), 7.33-7.45 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 65.2 ($\mathbf{C}H_2OH$), 70.0 ($O\mathbf{C}H_2Ph$), 101.2 (C4), 105.6 (C2 and C6), 127.4 (Ph), 127.9 (Ph), 128.4 (Ph), 136.7 (C1), 143.3 (Ph), 159.9 (C3 and C5).

(b) From compound 150

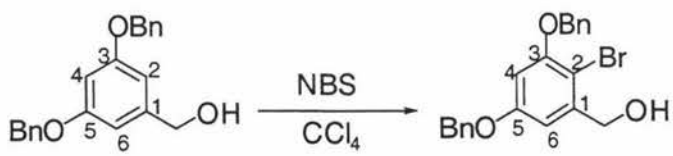


150 **151**

A solution of **150** (510.0 mg, 1.44 mmol, 1.0 equiv.) in THF (10 mL) was added slowly to a stirred suspension of $LiAlH_4$ (54.6 mg, 1.44 mmol, 1.0 equiv.) in THF (10 mL) under an atmosphere of nitrogen. The mixture was stirred at room temperature for 2 h before another portion of $LiAlH_4$ (54.6 mg, 1.44 mmol. 1.0 equiv) was added. After 15 min the reaction was quenched with methanol (1 mL) and stirred for a further 5 min. The mixture was then diluted with ethyl acetate (25 mL), washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield compound **151** (369.4 mg, 80%) as a colourless solid. Data as above

3,5-*bis*(Benzoxy)-2-bromobenzyl alcohol (146)[6]

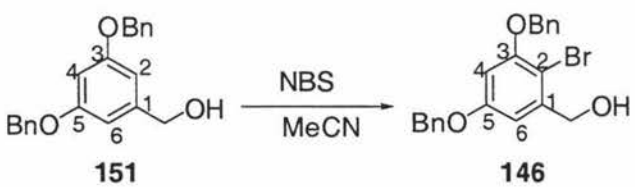
(a) With carbon tetrachloride as solvent



151 **146**

Compound **151** (309.0 mg, 0.96 mmol, 1.o equiv) was dissolved in warm CCl_4 (5 mL) and the solution was cooled to room temperature. Portions of NBS (171.9 mg, 0.96 mmol 1.0 equiv) were added with stirring. The mixture was heated at gentle reflux under nitrogen for 40 min and cooled to room temperature, resulting in the formation of a colourless precipitate. The reaction mixture was diluted with CH_2Cl_2 (20 mL) to produce a clear solution and washed with 1 M NaOH (30 mL), water (until the aqueous layer became neutral), brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give compound **146** (361.3 mg, 95%) as a colourless solid. R_f 0.54 (1:1 Hex/EtOAc). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.51 (s, 1H, O**H**), 4.71 (s, 2H, C**H**$_2$OH), 5.01 (s, 2H, OC**H**$_2$Ph), 5.08 (s, 2H, OC**H**$_2$Ph), 6.55 (d, J = 2.6 Hz, 1H, H4), 6.81 (d, J = 2.6 Hz, 1H, H6), 7.34-7.50 (m, 10H, Ar-H). ^{13}C NMR ($CDCl_3$, 270 MHz) δ 65.0 (**C**H$_2$OH), 70.2 (O**C**H$_2$Ph), 70.7 (O**C**H$_2$Ph), 101.0 (C4), 102.9 (C2), 105.9 (C6), 126.8, 127.4 (OCH$_2$**Ph**), 127.9, 128.1 (OCH$_2$**Ph**), 128.4, 128.4 (OCH$_2$**Ph**), 136.2 (OCH$_2$**Ph**), 136.3 (OCH$_2$**Ph**), 141.7 (C1), 155.3 (C5), 158.7 (C3).

(b) With acetonitrile as solvent

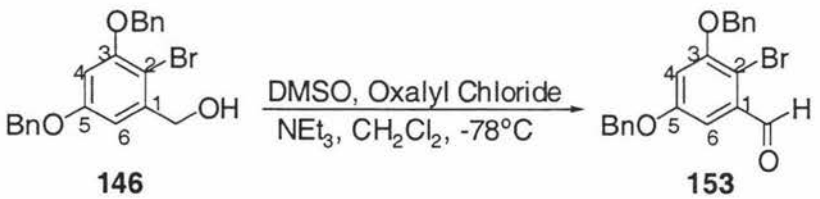


151 **146**

Portions of NBS (238.6 mg, 1.34 mmol, 1.0 equiv.) were added slowly to a stirred solution of compound **151** (428.9 mg, 1.34 mmol, 1.0 equiv.) in MeCN (15 mL). The mixture was heated at a gentle reflux under N_2 for 40 min, then cooled to room temperature. The

mixture was diluted with ethyl acetate (40 mL), washed with 1M NaOH (40 mL), water (until the aqueous layer was neutral), brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give compound **146** (520 mg, 97%) as a colourless solid. Data as above.

3,5-*bis*(Benzoxy)-2-bromobenzaldehyde (153)

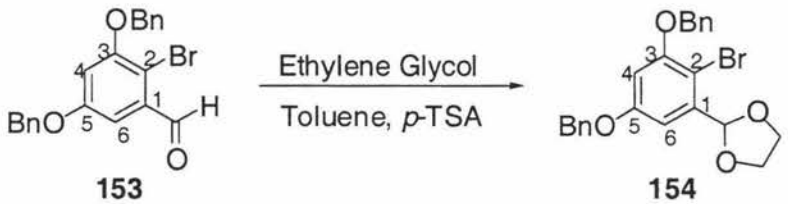


146 **153**

A solution of DMSO (142 μL, 156.7 mg, 2.01 mmol, 4.0 equiv.) in CH_2Cl_2 (15 mL) was cooled to –78 °C. Oxalyl chloride (87.8 μL, 127.3 mg, 1.00 mmol, 2 equiv.) was added dropwise and the mixture stirred under an atmosphere of nitrogen for 20 min. A solution of **146** (210.3 mg, 0.50 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was added slowly and stirring continued for a further 30 min. Triethylamine (69.9 μL, 507.3 mg, 5.01 mmol, 10 equiv.) was added, the mixture warmed to room temperature and stirred for 1 h. The mixture was diluted with CH_2Cl_2 (80 mL), washed with 2 M HCl until the pH was 6 according to UIP. The solution was further washed with sat'd aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give compound **153** as a colourless crystalline solid (quant). R_f 0.82 (1:1 Hex/EtOAc). ^{1}H NMR ($CDCl_3$, 270 MHz), δ 5.06 (s, 2H, OC**H**$_2$Ph), 5.14 (s, 2H, OC**H**$_2$Ph), 6.84 (d, J= 2.6 Hz, 1H, Ar-H), 7.16 (d, J = 2.8 Hz, 1H, Ar-H), 7.35-7.49 (m, 10H, Ph), 10.43 (s, 1H, aldehyde); ^{13}C NMR ($CDCl_3$, 270 MHz), δ 70.5, 71.1 (O**C**H$_2$Ph),

104.9, 107.8 (C2), 109.9 (C2), 126.9, 127.6, 128.1, 128.2, 128.6 (Ph), 134.6, 135.6, 135.8 (C1, Ph), 156.0, 158.7 (C3, C5), 191.7 (COH).

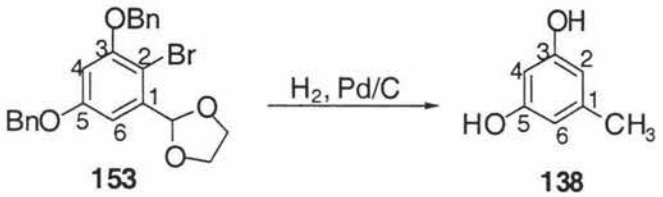
2-(3',5'-dibenzoxy-2'-bromophenyl)-1,3-dioxolane (154)[7]



153 **154**

A solution of compound **153** (827.6 mg, 2.09 mmol, 1.0 equiv) and ethylene glycol (315 μL, 349.5 mg, 5.63 mmol, 2.7 equiv) in toluene (10 mL), with a catalytic amount of *p*-toluene sulfonic acid (3 mg) was heated at reflux with a Dean-Stark apparatus for 24 h. The reaction mixture was washed with sat'd aq. $NaHCO_3$ (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with 5:1 hexane/ethyl acetate afforded compound **154** (779 mg, 85%) as a colourless solid. R_f 0.35 (3:1 Hex/EtOAc). ^1H NMR ($CDCl_3$, 270 MHz) δ 4.03–4.20 (m, 4H, OC**H**$_2$C**H**$_2$), 5.05 (s, 2H, OC**H**$_2$Ph), 5.11 (s, 2H, OC**H**$_2$Ph), 6.20 (s, 1H, ArC**H**), 6.65 (d, J = 2.9 Hz, 1H, H4), 6.96 (d, J = 2.9 Hz, 1H, H6) 7.22-7.59 (m, 10H, Ar-H). ^{13}C NMR ($CDCl_3$, 270 MHz) δ 65.3 (O**C**H$_2$**C**H$_2$O), 70.2 (O**C**H$_2$Ph), 70.8 (O**C**H$_2$Ph), 102.3, 102.7, 105.0, 104.4 (C4, C6, Ar**C**H, C2), 126.8, 127.4, 127.7, 127.9, 128.3, 128.4, 136.1, 136.2 (Ph), 138.4 (C1), 155.6 (C5), 156.6 (C3). HRMS (FAB^+, NBA, CH_2Cl_2) calculated for $C_{23}H_{22}O_4Br$ (MH^+): 443.068099, observed: 443.067368.

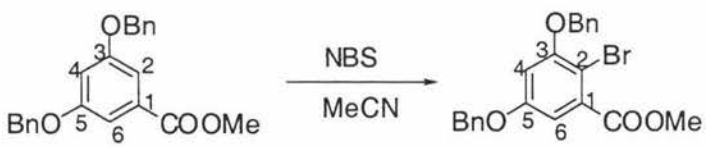
Methyl 3,5-dihydroxybenzene (138)[8]



153 138

A solution of compound **153** (99.8 mg, 0.23 mmol) and 10% Pd/C (50 mg) in ethanol (5 mL) was stirred under an atmosphere of H_2(g) for 3 h at room temperature. The reaction mixture was filtered through Celite, rinsing with ethanol. The filtrate was concentrated *in vacuo* to give an orange oil (48.9 mg, 120%). LRMS (EI^+, MeOH) m/z 124

Methyl 3,5-*bis*(Benzoxy)-2-bromobenzoate (156)

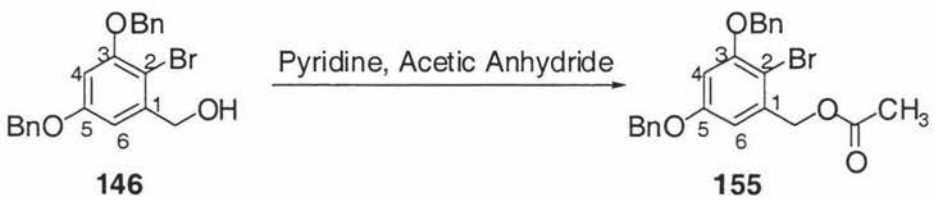


150 156

Portions of NBS (103.5 mg, 0.58 mmol, 1.0 equiv.) were added slowly to a stirred solution of compound **150** (202.3 mg, 0.58 mmol, 1.0 equiv.) in MeCN (10 mL). The mixture was heated at gentle reflux under N_2 for 40 min, then cooled to room temperature. The mixture was diluted with ethyl acetate (30 mL), washed with 1M NaOH (30 mL), water (until the aqueous layer was neutral), brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give compound **156** (52 mg, 82%) as a colourless solid. R_f 0.51 (1:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 270 MHz), δ 3.93 (s, 3H, COOC**H**$_3$) 5.08 (s, 2H, OC**H**$_2$Ph), 5.11 (s, 2H, OC**H**$_2$Ph), 6.69 (d, J = 2.8 Hz, 1H, H2/H4), 6.92 (d, J = 2.8 Hz, 1H, H6), 7.29-7.50 (m, 10H, Ar-H).

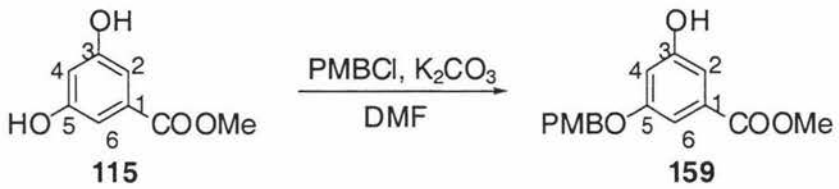
3,5-*bis*(Benzoxy)-2-bromobenzyl acetate (155)[9]



146 **155**

Acetic anhydride was added dropwise to a solution of compound **146** (87.7 mg, 0.22 mmol) in pyridine (3 mL). The solution was stirred under an atmosphere of N_2(g) at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate (10 mL), washed with 2M HCl (10 mL), sat'd aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with 3:1 hexanes/ethyl acetate to give compound **155** as a colourless solid (83.0 mg, 96%). R_f 0.60 (1:1 Hex/EtOAc). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.11 (s, 3H, OC**H**$_3$), 5.00 (s, 2H, OC**H**$_2$Ar), 5.08 (s, 2H, OC**H**$_2$Ar), 5.17 (s, 2H, OC**H**$_2$Ar), 6.56 (d, J = 2.6 Hz, H4/H6), 6.67 (d, J = 2.8 Hz, H4/H6), 7.30-7.50 (m, 10H Ar-H). ^{13}C NMR ($CDCl_3$, 270 MHz) δ 20.9 (**C**H$_3$O), 65.9 (**C**H$_2$OAC), 70.3, 70.8 (**C**H$_2$Ph), 101.4 (C4), 104.2 (C2), 107.3 (C6), 126.8, 127.4, 127.8, 128.1, 128.2, 128.5, 128.5, 136.1, 136.2 (OCH$_2$**Ph**), 137.0 (C1), 155.7 (C5), 158.6 (C3), 170.3 (O**C**OCH$_3$).

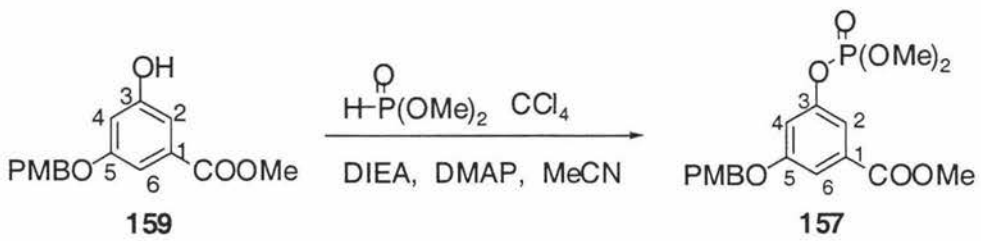
Methyl 3-Hydroxy-5-(*p*-methoxybenzoxy)benzoate (159)



115 **159**

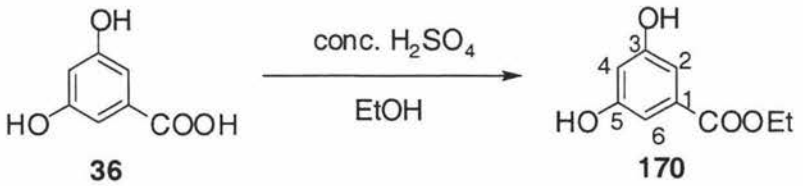
p-Methoxybenzyl chloride (187.6 mg, 1.19 mmol, 1.0 equiv) was added slowly to a suspension of **115** (201 mg, 1.19 mmol, 1.0 equiv.) and K_2CO_3 (414 mg, 2.99 mmol, 2.5 equiv) in DMF (10 mL) and stirred under an atmosphere of $N_2(g)$ for 72 h at room temperature. The reaction mixture was diluted with EtOAc (50 mL), washed with H_2O (2 x 50 mL) and brine, dried over $MgSO_4$, filtered and concentrated down *in vacuo*. Flash column chromatography of the residue, eluting with 5:1 hexane/ethyl acetate afforded methyl 3,5-di (*p*-methoxybenzoxy)benzoate (**160**) (178 mg, 36%) as a colourless solid. R_f 0.19 (3:1 Hex/EtOAc) ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.80 (s, 6H, C**H**$_3$O), 3.90 (s, 3H, COOC**H**$_3$), 4.99 (s, 4H, OC**H**$_2$Ar), 6.78 (t, *J* = 2.2 Hz, 1H, H4), 6.90 (d, *J* = 8.8 Hz, 4H, Ar-H, *ortho* to OCH_3), 7.28 (d, *J* = 2.4 Hz, 2H, H2, H6), 7.33 (d, *J* = 8.8 Hz, 4H, Ar-H, *ortho* to CH_2OR). Further elution gave the desired monoprotected compound **159** (106.0 mg, 31%) as a colourless solid. R_f 0.36 (3:1 Hex/EtOAc), ^{1}H NMR ($CDCl_3$, 270 MHz), δ 1.37 (t, *J* = 7.0 Hz, 3H, $COOCH_2CH_3$), 3.81 (s, 3H, OC**H**$_3$), 4.35 (q, *J* = 7.0 Hz, 2H, COOC**H**$_2$CH$_3$), 4.96 (s, 2H, OC**H**$_2$Ar), 6.67 (t, *J* = 2.2 Hz, 1H, H4), 6.90 (d, *J* = 8.78 Hz, 2H, Ar-H, *ortho* to OCH_3), 7.15-7.25 (m, 2H, H2, H6), 7.32 (d, *J* = 8.8 Hz, 2H, Ar-H, *ortho* to CH_2OR). The elutant was changed to 1:1 hexane/ethyl acetate and starting material was recovered.

Methyl 3-dimethylphosphate-5-(*p*-methoxybenzoxy)benzoate (157)



Carbon tetrachloride (1.05 mL, 6.92 mmol, 5.0 equiv.) was added to a solution of **159** (421.0 mg, 1.39 mmol, 1.0 equiv.) in MeCN (10 mL) at –10 °C and stirred for 5 min under an atmosphere of nitrogen. Diisopropylethylamine (0.51 mL, 2.91 mmol, 2.1 equiv.) and DMAP (17 mg, 0.14 mmol, 0.1 equiv.) were added and the solution stirred for a further 1 min. Dimethylphosphite (0.184 mL, 2.01 mmol, 1.45 equiv.) was then added dropwise maintaining a temperature of -10 °C and left to stir for approximately 45 min. The solution was diluted with ethyl acetate (50 mL), washed with water (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with 3:1 hexane/ethyl acetate afforded the phosphorylated compound **157** (0.454 g, 80%) as a colourless oil. R_f 0.29 (1:1 Hex/EtOAc). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.80 (s, 3H COOC**H**$_3$), 3.83 (s, 3H, OC**H**$_3$), 3.89 (d, J = 5 Hz, 6H, P(OC**H**$_3$)$_2$), 5.00 (s, OC**H**$_2$Ar), 6.91 (d, J = 8.8 Hz, 2H, Ar-PMB), 7.00-7.10 (m, 1H, H4), 7.35 (d, J = 8.6 Hz, 2H, Ar-PMB), 7.40-7.50 (m, 2H, H2, H6); ^{13}C NMR ($CDCl_3$, 270 MHz), δ 52.4 (COOC**H**$_3$), 54.97 (d, J = 6 Hz, P(O**C**H$_3$)$_2$), 55.2 (**C**H$_3$O), 70.3 (O**C**H$_2$Ar), 111.8 (d, J = 4 Hz, C2/C4) 112.3 (C6), 113.4 (d, J = 5 Hz, C2/C4), 113.9 (PMB), 127.9 (PMB) 129.2 (PMB) 132.3 (C1), 151.1 (d, J = 7 Hz, C3), 159.5 (d, J = 5 Hz, C5), 165.7 (**C**OOCH$_3$).

Ethyl 3,5-dihydroxybenzoate (170)[10]



36 **170**

A solution of α–resorcylic acid (**36**) (2.50 g, 16 mmol) in ethanol (20 mL) was treated with concentrated sulfuric acid (0.2 mL) and heated at reflux for 5 h. The ethanol was removed *in vacuo* and the residue taken up in ethyl acetate (60 mL). The solution was washed successively with sat'd aq. $NaHCO_3$ (60 mL), water (60 mL) and brine (60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the methyl ester (**168**) as a colourless solid (2.74 g, 94%). R_f 0.45 (1:1 hex/EtOAc). ^{1}H NMR (CD_3OD, 270 MHz) δ 1.33 (t, J = 7.3 Hz, 3H, $COOCH_2C\mathbf{H}_3$), 4.28 (q, J = 7.3 Hz, 2H, $COOC\mathbf{H}_2CH_3$), 6.48 (t, J = 2.2 Hz, 1H, H4) 6.93 (d, J= 2.2 Hz, 2H, H2, H6); ^{13}C NMR (CD_3OD, 270 MHz) δ 13.6 ($COOCH_2\mathbf{C}H_3$), 61.0 ($COO\mathbf{C}H_2CH_3$), 107.1 (C4), 107.7 (C2, C6), 132.2 (C1), 158.5 (C3, C5), 167.0 ($\mathbf{C}OOCH_2CH_3$).

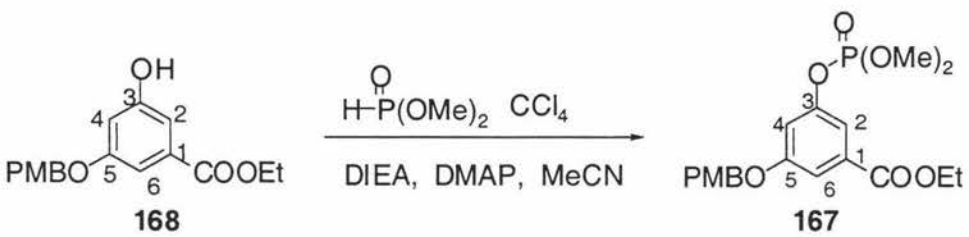
Ethyl 3-hydroxy-5-(*p*-methoxybenzoxy)benzoate (168)

170 **168** **171**

p-Methoxybenzyl chloride (2.287 g, 2.03 mL, 14.6 mmol, 1.0 equiv.) was added slowly to a suspension of compound **170** (2.6587 g, 14.6 mmol, 1.0 equiv.) and K_2CO_3 (5.0475 g, 36.0 mmol, 2.5 equiv.) in DMF (20 mL) and stirred under an atmosphere of N_2 for 72 h at room temperature. The reaction mixture was diluted with EtOAc (50 mL), washed with H_2O (2 x 50 mL) and brine, dried over $MgSO_4$ filtered and concentrated down *in vacuo*. Flash column chromatography of the residue, eluting with 5:1 hexanes/ethyl acetate afforded ethyl 3,5-di-(*p*-methoxybenzyloxy)benzoate **171** (2.156 g, 35%) as a colourless solid. R_f 0.38 (3:1 Hex/EtOAc) ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.41 (t, *J* = 7.0 Hz, 3H, $COOCH_2C\mathbf{H}_3$), 3.79 (s, 6H, $C\mathbf{H}_3O$), 4.38 (q, *J* = 7.0 Hz, 2H, $COOC\mathbf{H}_2CH_3$), 4.99 (s, 2H, $OC\mathbf{H}_2Ar$), 6.78 (t, *J* = 2.2 Hz, 1H, H4), 6.90 (d, *J* = 8.8 Hz, 4H, Ar-H, *ortho* to OCH_3), 7.28 (d, *J* = 2.4 Hz, 2H, H2, H6), 7.33 (d, *J* = 8.8 Hz, 4H, Ar-H, *ortho* to CH_2OR). ^{13}C NMR ($CDCl_3$, 270 MHz) δ 14.3 ($COOCH_2\mathbf{C}H_3$), 55.2 ($O\mathbf{C}H_2(C_6H_4)OCH_3$), 61.0 ($O\mathbf{C}H_2CH_3$), 70.0 ($\mathbf{C}H_3O(C_6H_4)$), 106.9 (C4), 108.2 (C2), 113.9, 129.1 ($CH_3O(\mathbf{C}_6H_4)$), 128.4 ($CH_3Oq(C_6H_4)$), 132.2 (C1), 159.3, 159.6 (C3, $CH_3O(C_6H_4)q$), 166.0 ($\mathbf{C}OOCH_2CH_3$). HRMS (FAB^+, NBA, MeOH) calculated for $C_{25}H_{26}O_6$ (MH^+): 422.172939, observed: 422.173848. Further elution gave the desired monoprotected compound **168** (1.413 g, 32%) as a colourless solid. R_f 0.19 (3:1 Hex/EtOAc). ^{1}H NMR ($CDCl_3$, 270 MHz), δ 1.37 (t, *J* = 7.0 Hz, 3H, $COOCH_2C\mathbf{H}_3$). 3.81 (s, 3H, $OC\mathbf{H}_3$), 4.35 (q, *J* = 7.0 Hz, 2H, $COOC\mathbf{H}_2CH_3$), 4.96 (s, 2H, $OC\mathbf{H}_2Ar$), 6.67 (t, *J* = 2.2 Hz, 1H, H4), 6.90 (d, *J* = 8.78 Hz, 2H, Ar-H, *ortho* to OCH_3), 7.15-7.25 (m, 2H, H2, H6), 7.33 (d, *J* = 8.8 Hz, 2H, Ar-H, *ortho* to CH_2OR); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 14.3 ($COOCH_2\mathbf{C}H_3$), 55.3 ($O\mathbf{C}H_2Ar$), 61.3 ($O\mathbf{C}H_2CH_3$), 70.0 ($\mathbf{C}H_3O$), 107.3, 107.9, 109.4 (C2, C4, C6), 114.0, 129.2 (Ar), 128.4 (Ar), 132.1 (C1), 156.9, 159.4, 159.8 (C3, C5, Ar), 166.5 ($\mathbf{C}OOCH_2CH_3$). The elutant was

changed to 1:1 hexane/ethyl acetate and starting material was recovered. HRMS (FAB^+, NBA, CH_2Cl_2) calculated for $C_{17}H_{18}O_5$ (MH^+): 302.115424, observed: 302.116944.

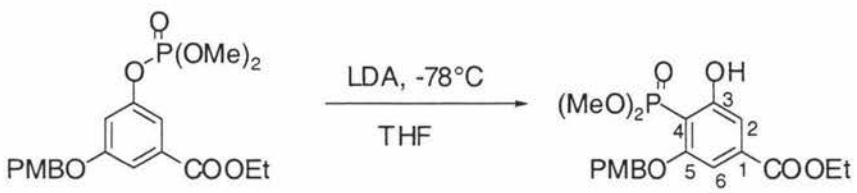
Ethyl 3-dimethylphosphate-5-(*p*-methoxybenzoxy)benzoate (167)



Carbon tetrachloride (2.16 mL, 3.44 g, 22 mmol, 5.0 equiv.) was added to a solution of **168** (1.3525 g, 4.48 mmol, 1.0 equiv.) in MeCN (10 mL) at –10 ° C and stirred for 5 min under an atmosphere of nitrogen. Diisopropylethylamine (1.64 mL, 1.22 g, 9.38 mmol, 2.1 equiv.) and DMAP (55 mg, 0.45 mmol, 0.1 equiv.) were added to the solution and stirred for a further 1 min. Dimethylphosphite (0.59 mL, 0.715 g, 6.49 mmol, 1.45 equiv.) was then added dropwise maintaining a temperature of <-10 °C and left to stir for approximately 45 min after the addition was complete. The solution was diluted with ethyl acetate (50 mL), washed with water (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with 3:1 hexanes/ethyl acetate afforded the phosphorylated compound **167** (1.66 g, 91%) as a colourless oil. R_f 0.24 (1:1 Hex/EtOAc). ^1H NMR ($CDCl_3$, 270 MHz) δ 1.39 (t, J = 7.0 Hz, 3H, $COOCH_2C\mathbf{H}_3$), 3.82, 3.85, 3.89 (s, 3H, $C\mathbf{H}_3OPh$, $PO(OC\mathbf{H}_3)_2$), 4.37 (q, J = 7.0 Hz, 2H, $COOC\mathbf{H}_2CH_3$), 5.02 (s, $OC\mathbf{H}_2(C_6H_4)$), 6.92 (d, J = 8.8 Hz, 2H, Ar-H, *ortho* to OCH_3), 7.06 (td, J = 2.2, 1.1 Hz, 1H, H4), 7.36 (d, J = 8.8 Hz, 2H, Ar-H, *ortho* to CH_2OR), 7.44-746

(m, 1H, H2), 7.48-7.52 (m, 1H, H6); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 14.3 ($OCH_2\mathbf{C}H_3$), 55.0 (d, J = 6.0 Hz, $PO(O\mathbf{C}H_3)_2$), 55.3 ($O\mathbf{C}H_2(C_6H_4)$), 61.4 ($O\mathbf{C}H_2CH_3$), 70.3 ($\mathbf{C}H_3O$), 111.6 (d, J = 5 Hz, C2 or 4), 112.4 (C6), 113.7 (d, J = 5 Hz, C2 or 4), 114.0, 127.9, 129.3 (C_6H_4), 132.7 (C1), 151.1 (d, J = 7 Hz, C3), 159.5 (C5 and $CH_3O(C_6H_4)$), 165.3 ($\mathbf{C}OOCH_2CH_3$). HRMS (FAB^+, NBA, MeOH) calculated for $C_{19}H_{24}O_{48}P$ (MH^+): 411.120881, observed: 411.119327.

Ethyl 4-dimethylphosphonate-3-hydroxy-5-(*p*-methoxybenzoxy)benzoate (166)



167 **166**

n-BuLi (316 μL, 2 M in hexane, 0.63 mmol, 1.3 equiv) was added slowly to a solution of diisopropylamine (88 μL, 64 mg, 0.63 mmol, 1.3 equiv.) in THF (5 mL) at –78°C and stirred under an atmosphere of N_2 for 15 min in flame-dried glassware. A solution of the phosphate **167** (199.6 mg, 0.49 mmol, 1.0 equiv) in THF (5 mL) was added slowly and stirred for 1 h at –78°C. The reaction mixture was diluted with sat'd aq. NH_4Cl (50 mL) and extracted with ethyl aetate (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography of the residue, eluting with 3:1 hexane/ethyl acetate afforded compound **166** (153.2 mg, 76%) as a colourless solid. R_f 0.20 (3:1 Hex/EtOAc).

^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.39 (t, *J* = 7 Hz, 3H, $COOCH_2C\mathbf{H}_3$), 3.69, (d, *J* = Hz, 6H, $PO(OC\mathbf{H}_3)_2$) 3.82 (s, 3H, $C\mathbf{H}_3O$), 4.38 (q, *J* = 7 Hz, 2H, $COOC\mathbf{H}_2CH_3$), 5.10 (s, 2H, OCH_2Ar), 6.92 (d, *J* = 8.6 Hz, 2H, H2'), 7.03 (dd, *J* = 5.5 Hz, 1.3 Hz, 1H, H2/H6), 7.11 (dd, *J* = 5.5 Hz, 1.1 Hz, 1H, H2/H6), 7.37 (d, *J* = 8.6 Hz, 2H, H3'), 11.32 (d, *J* = 1.3 Hz, 1H, O**H**); ^{13} C NMR ($CDCl_3$, 270 MHz) δ 13.9 ($COOCH\mathbf{C}H_3$), 53.3 (d, *J* = 5.4 Hz, $P(O\mathbf{C}H_3)_2$), 55.1 ($ArO\mathbf{C}H_3$), 61.4 ($COO\mathbf{C}H_2CH_3$), 70.4 ($O\mathbf{C}H_2Ar$), 100.3 (d, *J* = 177 Hz, C4), 102.4 (d, *J* = 8.4 Hz, C2/C6), 111.7 (d, *J* = 12.3 Hz, C2/C6), 113.7 (C2'), 127.8 (C1'), 128.9 (C3'), 137.1 (C1), 159.4 (C4'), 160.8 (C5), 164.2 (d, *J* = 5.4 Hz, C3), 165.5 (**C**OOMe). HRMS (FAB^+, NBA, CH_2Cl_2) calculated for $C_{19}H_{23}O_8P$ (MH^+): 410.113056, observed: 410.116498.

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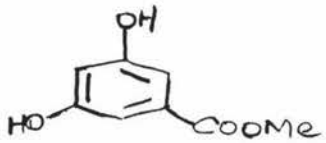

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RCVR gain	31
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
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PW02	
PW03	

Compound 115

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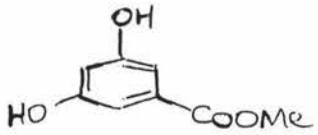

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Date	18/4/01

Compound 115

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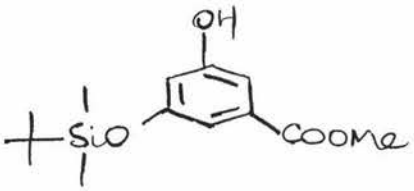
3:31 PM



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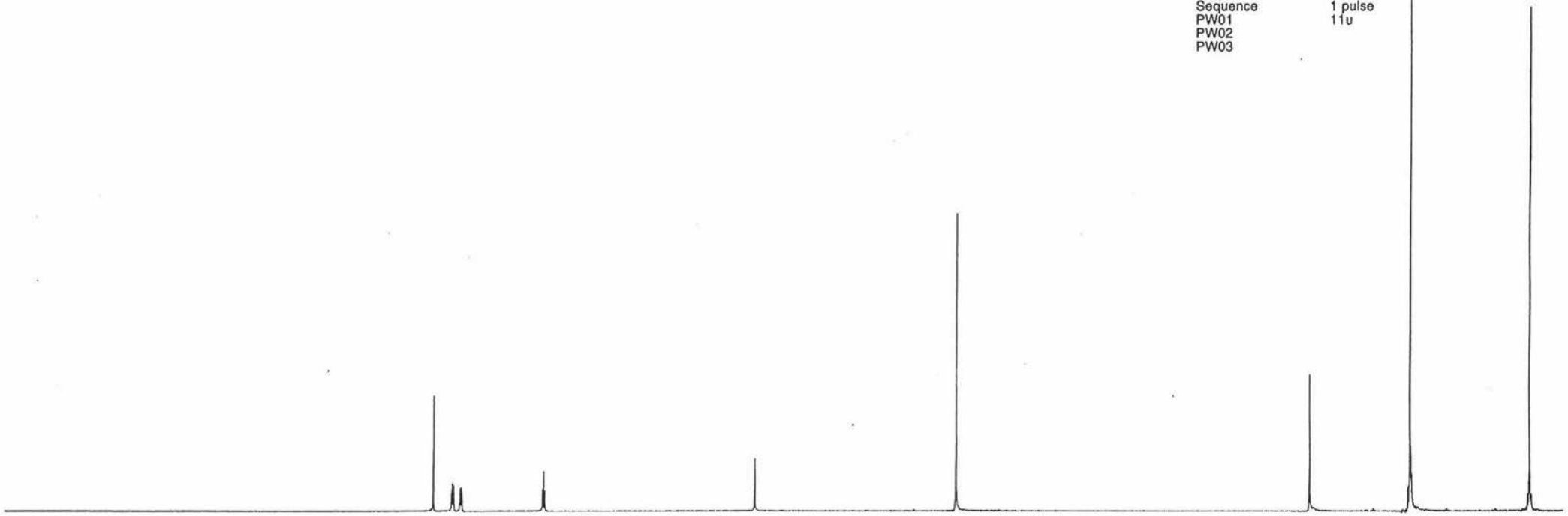
PW02	
PW03	



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Compound 116

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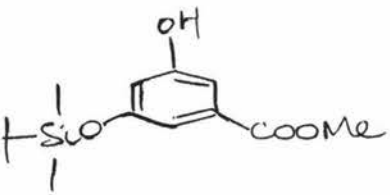

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spin rate	11
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LB 1D	2.00
Filename	Recrstyalised Phenol
Date	19/11/01

Compound 116

File created:
Monday, 19 November 2001
10:02 AM

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Acq. Points	16384
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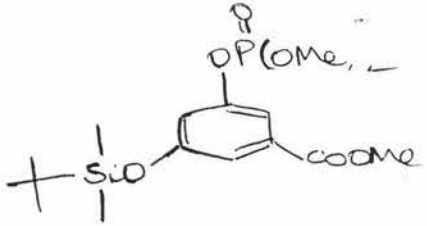

Compound 117

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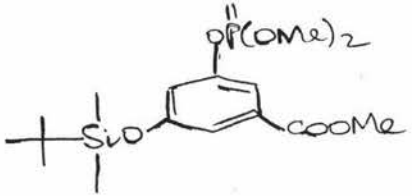
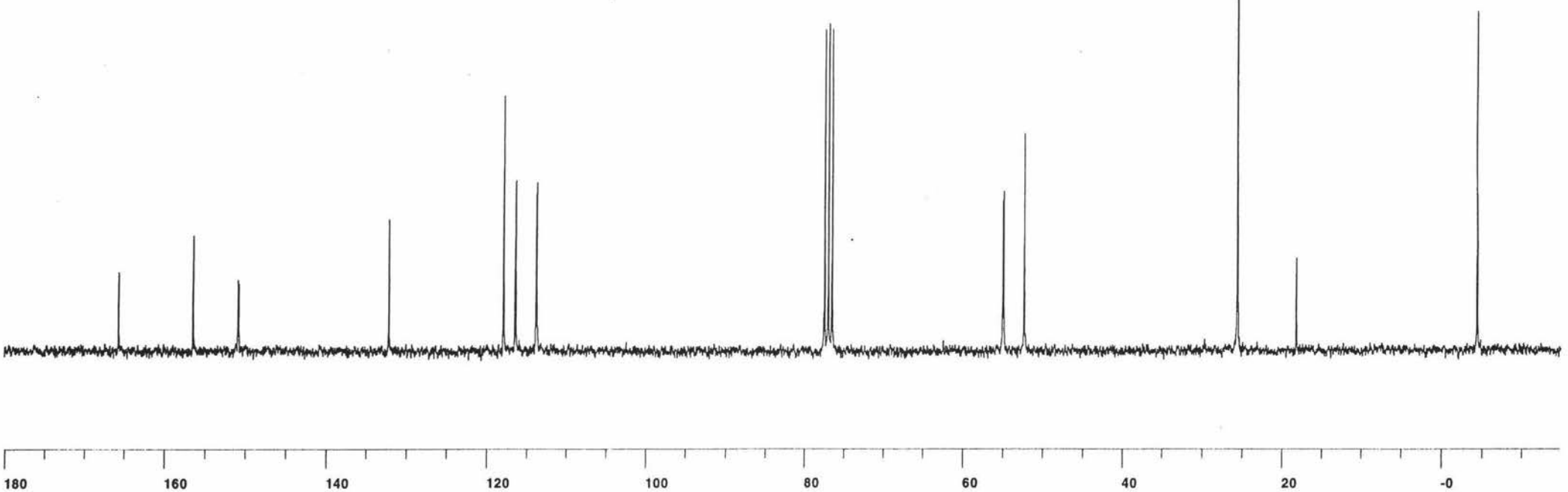
Thursday, 26 July 2001
2:41 PM

tecmag



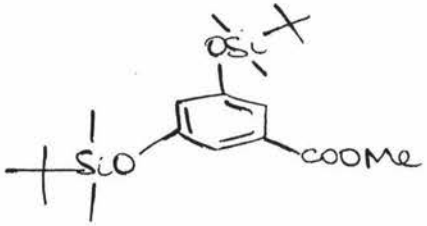
Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +l-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	1024
Dummy scan	0
Scan Count	601
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	14
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	phosPdt combined pg 22,24&25
Date	1/8/01



ppm

Compound 117

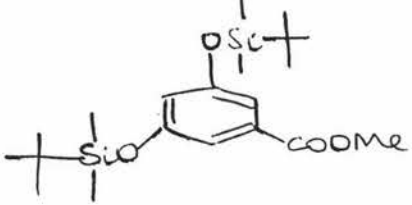
File created:
Wednesday, 1 August 2001
11:29 AM



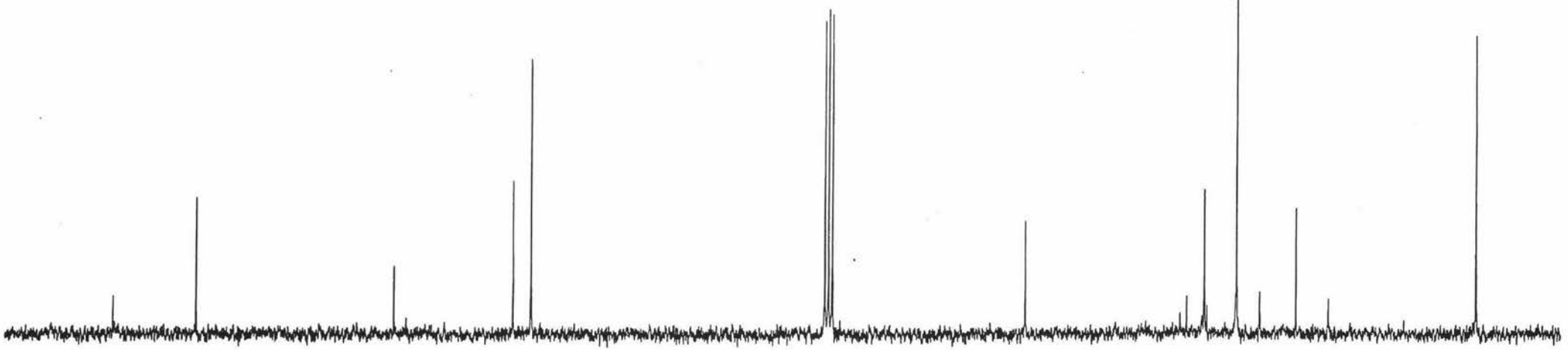
Nucleus	*H1
Dwell 1D	277.778u
SW +l-	1800.0
FILTER	1800
Scans 1D	8
Scan Count	8
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	28
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

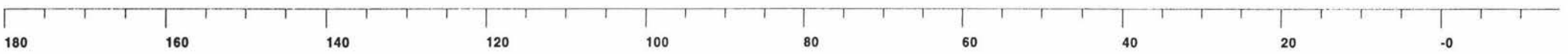
Compound 120

File created:
Thursday, 26 July 2001
2:45 PM



Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +l-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	256
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	11
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	Clean Unknown C13
Date	19/11/01

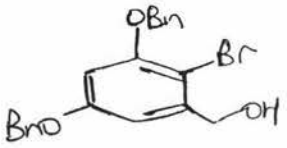




ppm

Compound 120

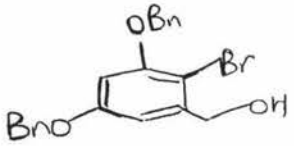
File created:
Monday, 19 November 2001
11:01 AM



Nucleus	*H1
Dwell 1D	277.778u
SW +/-	1800.0
FILTER	1800
Scans 1D	4
Scan Count	4
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	23
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

Compound 146

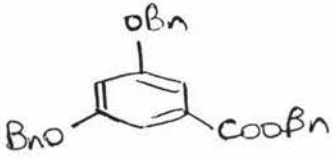
File created:
Wednesday, 13 February 2002
12:41 PM



Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +l-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	256
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	10
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	pg 49 NBS Br C
Date	13/2/02

Compound 146

File created:
Wednesday, 13 February 2002
12:46 PM

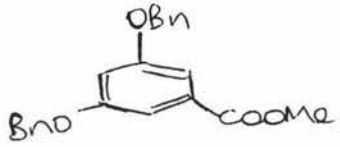


Nucleus	*H1
Dwell 1D	277.778u
SW +/-	1800.0
FILTER	1800
Scans 1D	4
Scan Count	4
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	25
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

ppm

Compound 149

File created:
Thursday, 29 August 2002
2:02 PM



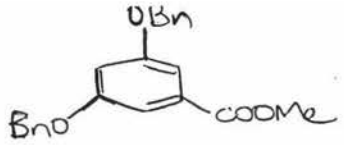
Nucleus	*H1
Dwell 1D	277.778u
SW +l-	1800.0
FILTER	1800
Scans 1D	8
Scan Count	8
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	28
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

10.0 8.0 6.0 4.0 2.0

ppm

Compound 150

File created:
Monday, 11 February 2002
1:10 PM

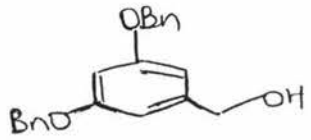


Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +l-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	256
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	10
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	pg47 benz C
Date	11/2/02

ppm

Compound 150

File created:
Monday, 11 February 2002
1:15 PM

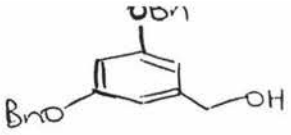


Nucleus	*H1
Dwell 1D	277.778u
SW +l-	1800.0
FILTER	1800
Scans 1D	4
Scan Count	4
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	25
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

ppm

Compound 151

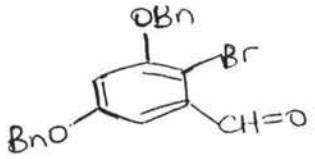
File created:
Tuesday, 12 February 2002
1:51 PM



Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +l-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	256
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	10
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	pg 48 reduction C
Date	12/2/02

Compound 151

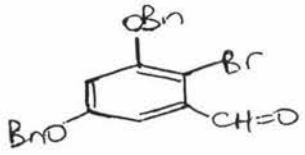
File created:
Tuesday, 12 February 2002
1:56 PM



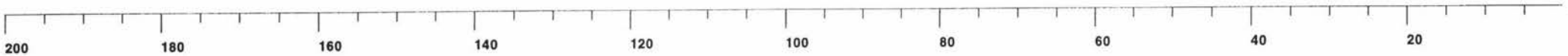
Nucleus	^{1}H1
Dwell 1D	277.778u
SW +I-	1800.0
FILTER	1800
Scans 1D	4
Scan Count	4
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	25
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

Compound 153

File created:
Wednesday, 6 March 2002
4:06 PM



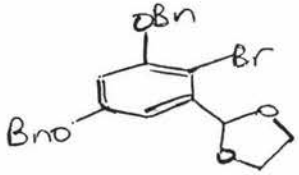
Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +l-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	236
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	5
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	aldehyde 1 C
Date	18/3/02



ppm

Compound 153

File created:
Monday, 18 March 2002
4:19 PM

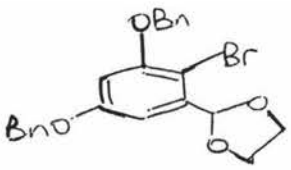


Nucleus	*H1
Dwell 1D	277.778u
SW +l-	1800.0
FILTER	1800
Scans 1D	4
Scan Count	4
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	21
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

ppm

Compound 154

File created:
Monday, 18 March 2002
4:48 PM

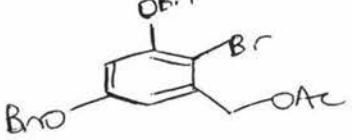


Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +l-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	207
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	11
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	acetal 1C
Date	18/3/02

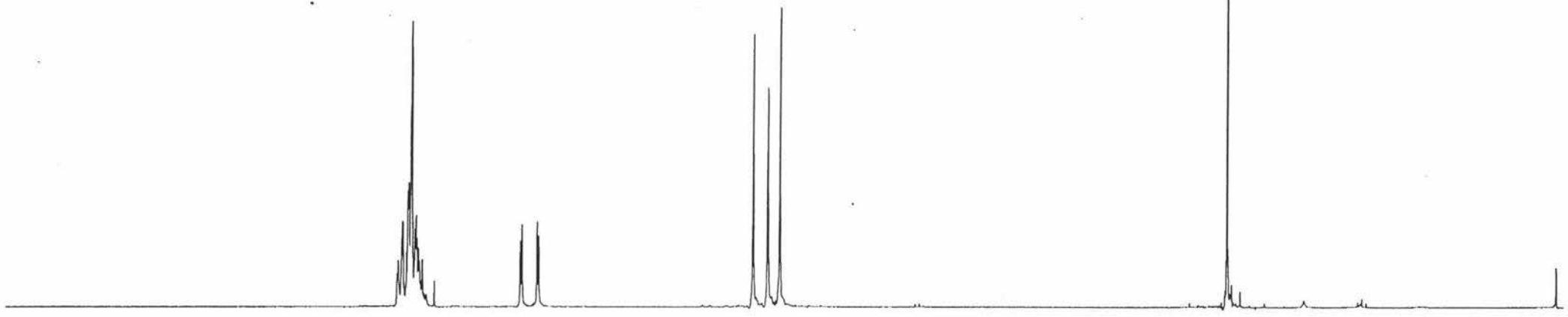
ppm

Compound 154

File created:
Monday, 18 March 2002
4:34 PM



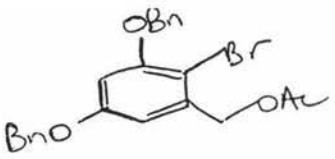
Nucleus	*H1
Dwell 1D	277.778u
SW +/-	1800.0
FILTER	1800
Scans 1D	4
Scan Count	4
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	25
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	



ppm

Compound 155

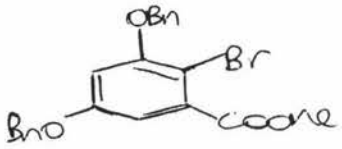
File created:
Friday, 13 September 2002
3:34 PM



Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +l-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	256
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	5
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	BK2 pg11 C13
Date	13/9/02

Compound 155

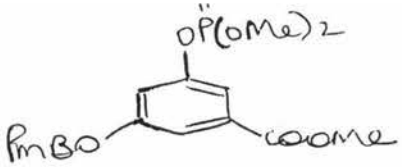
File created:
Friday, 13 September 2002
3:36 PM



Nucleus	*H1
Dwell 1D	277.778u
SW +I-	1800.0
FILTER	1800
Scans 1D	16
Scan Count	16
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	29
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

Compound 156

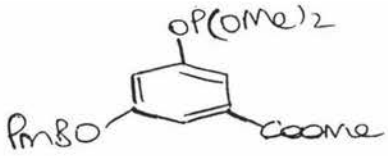
File created:
Friday, 1 March 2002
9:36 AM



Nucleus	*H1
Dwell 1D	277.778u
SW +/-	1800.0
FILTER	1800
Scans 1D	4
Scan Count	4
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	24
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

Compound 157

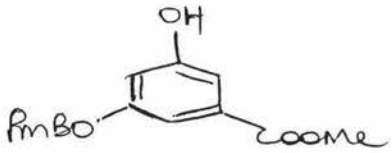
File created:
Wednesday, 5 June 2002
4:42 PM



Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +I-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	256
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	15
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	pg 75 AT PMB-C13
Date	6/6/02

Compound 157

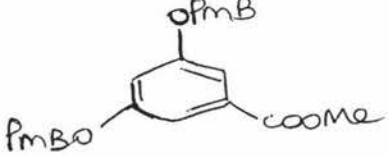
File created:
Thursday, 6 June 2002
2:49 PM



Nucleus	*H1
Dwell 1D	277.778u
SW +/-	1800.0
FILTER	1800
Scans 1D	8
Scan Count	8
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	27
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

Compound 159

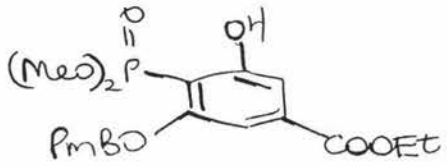
File created:
Monday, 6 May 2002
3:57 PM



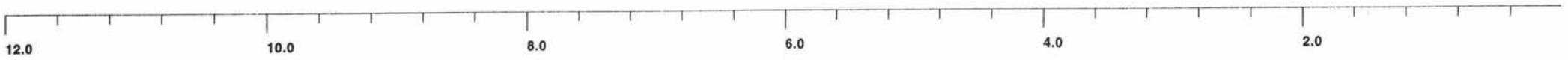
Nucleus	*H1
Dwell 1D	277.778u
SW +/-	1800.0
FILTER	1800
Scans 1D	4
Scan Count	4
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	24
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

Compound 160

File created:
Wednesday, 8 May 2002
4:41 PM



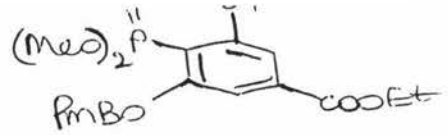
Nucleus	*H1
Dwell 1D	277.778u
SW +I-	1800.0
FILTER	1800
Scans 1D	16
Scan Count	16
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	32
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	



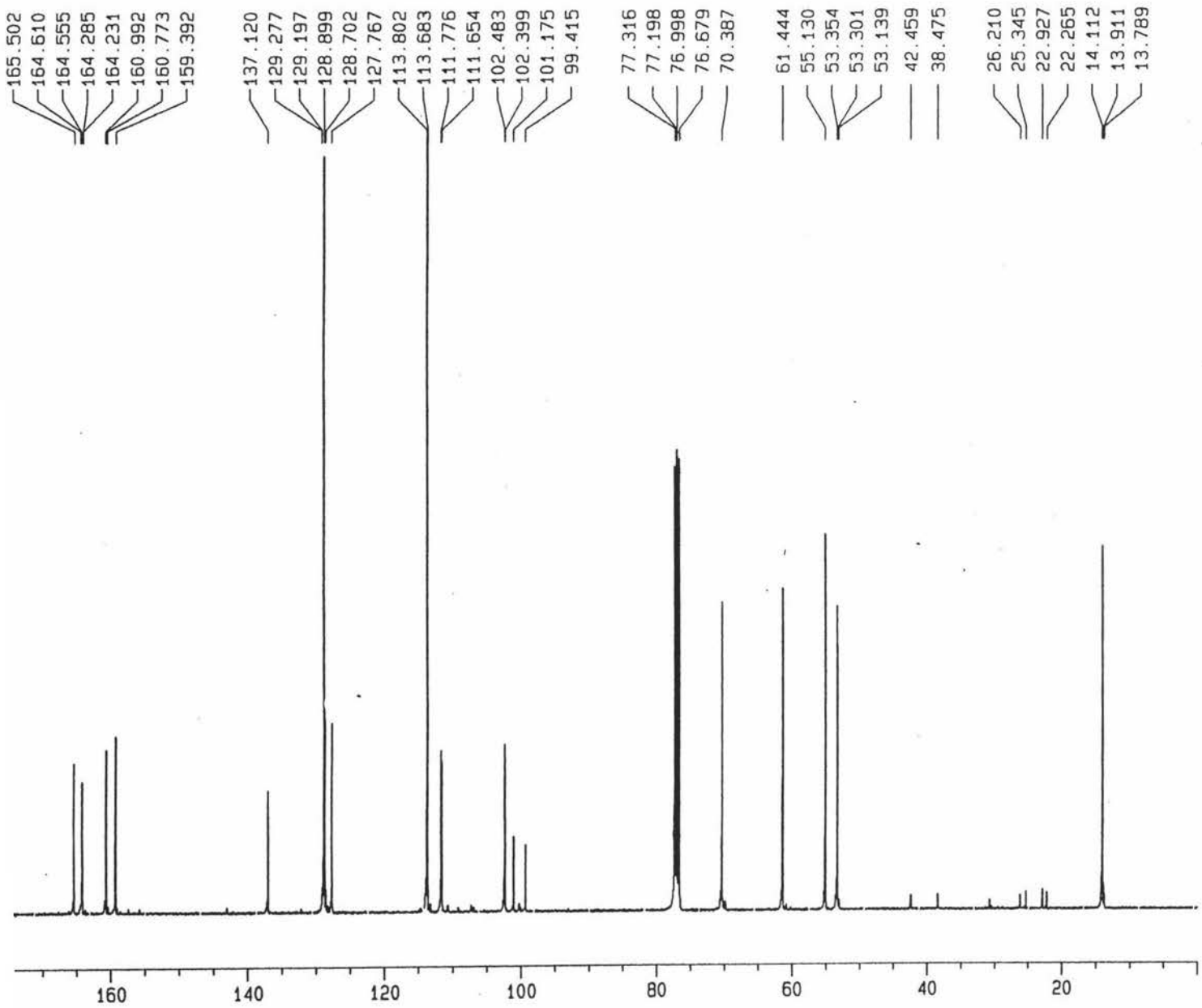
ppm

Compound 166

File created:
Friday, 18 October 2002
4:01 PM



Amy FINAL rearrangement
13C normal



Current Data Parameters

NAME	Amy
EXPNO	7
PROCNO	1

F2 - Acquisition Parameters

Date_	20021130
Time	14.46
INSTRUM	spect
PROBHD	5 mm QNP 1H/
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	15000
DS	4
SWH	25125.629 Hz
FIDRES	0.383387 Hz
AQ	1.3042164 sec
RG	4096
DW	19.900 usec
DE	6.00 usec
TE	300.0 K
D1	2.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec

---------- CHANNEL f1 ----------

NUC1	13C
P1	9.30 usec
PL1	0.00 dB
SFO1	100.6237959 MHz

---------- CHANNEL f2 ----------

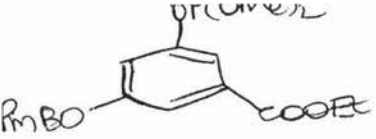
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	18.00 dB
PL13	22.00 dB
SFO2	400.1316005 MHz

F2 - Processing parameters

SI	32768
SF	100.6127794 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	180.000 ppm
F1	18110.30 Hz
F2P	-0.000 ppm
F2	-0.00 Hz
PPMCM	9.00000 ppm/cm
HZCM	905.51514 Hz/cm



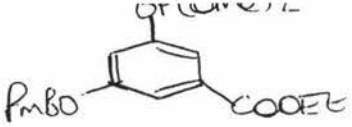
Nucleus	*H1
Dwell 1D	277.778u
SW +I-	1800.0
FILTER	1800
Scans 1D	8
Scan Count	8
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	27
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

10.0 8.0 6.0 4.0 2.0

ppm

Compound 167

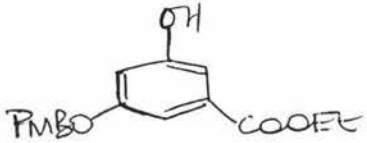
File created:
Thursday, 31 October 2002
1:12 PM



Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +l-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	256
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	5
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	BK2/25 AT-PMB C
Date	31/10/02

Compound 167

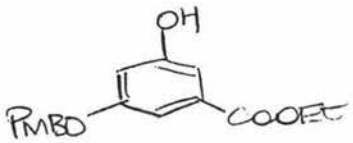
File created:
Thursday, 31 October 2002
1:15 PM



Nucleus	*H1
Dwell 1D	277.778u
SW +I-	1800.0
FILTER	1800
Scans 1D	8
Scan Count	8
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	28
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

Compound 168

File created:
Thursday, 31 October 2002
1:06 PM

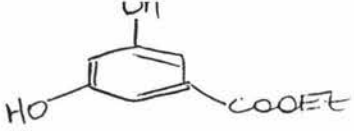


Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +l-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	256
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	16
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	BK2 pg 24 mono PMB C13
Date	31/10/02

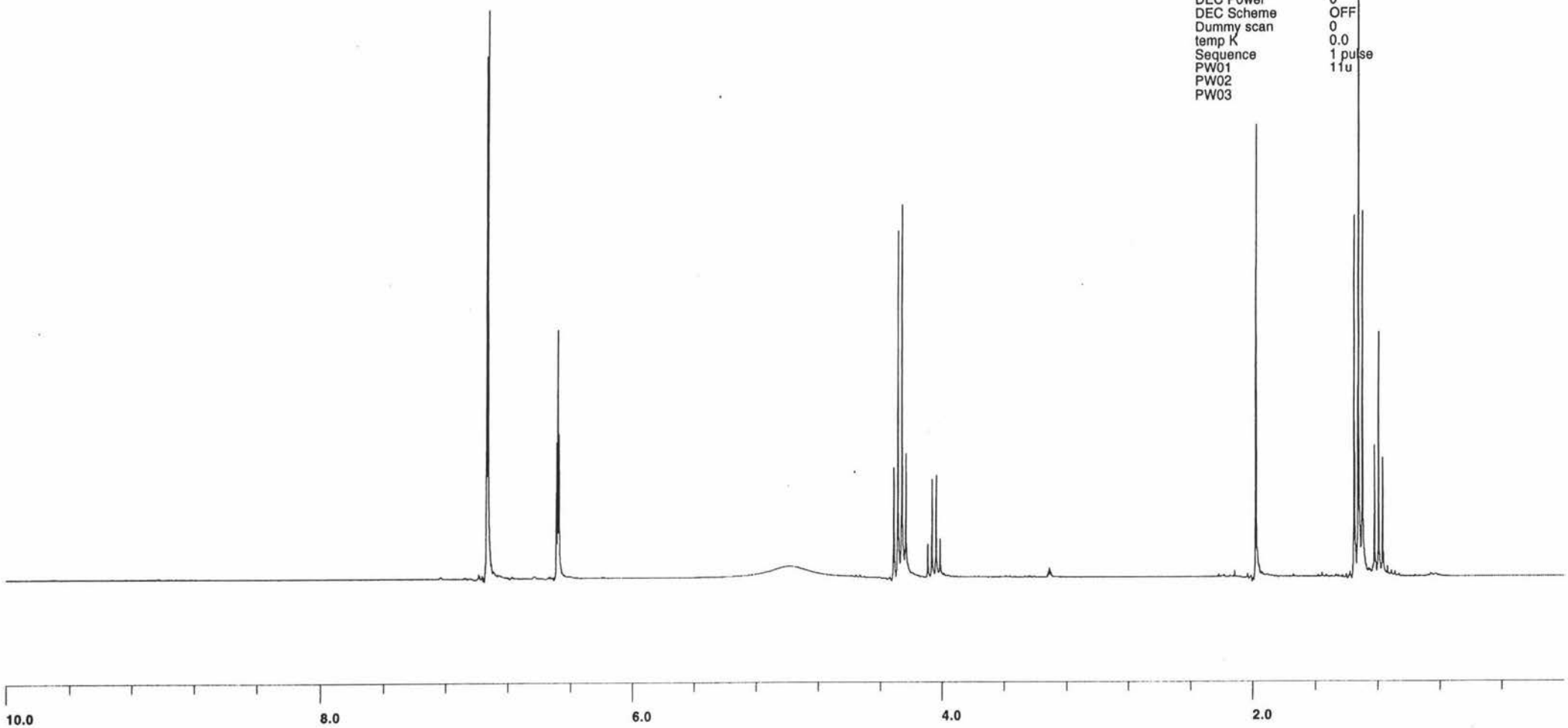
ppm

Compound 168

File created:
Thursday, 31 October 2002
4:12 PM

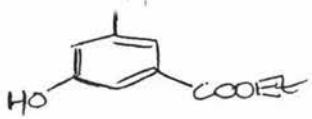


Nucleus	*H1
Dwell 1D	277.778u
SW +/-	1800.0
FILTER	1800
Scans 1D	4
Scan Count	4
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	24
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	



Compound 170

File created:
Tuesday, 23 July 2002
5:06 PM

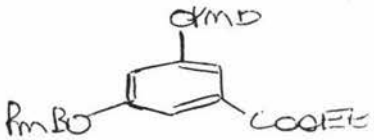


Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +l-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	256
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	0
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	89 ethyl ester C
Date	24/7/02

ppm

Compound 170

File created:
Wednesday, 24 July 2002
11:41 AM



Nucleus	*H1
Dwell 1D	277.778u
SW +l-	1800.0
FILTER	1800
Scans 1D	4
Scan Count	4
Points 1D	16384
Last Delay	2s
Obs Freq	270.1563574
F1 base	270.05 MHz
F1 offset	106.3574 KHz
RCVR gain	23
F2 freq	270.1910000
F2 base	270.05 MHz
F2 offset	141.0000 KHz
DEC Power	0
DEC Scheme	OFF
Dummy scan	0
temp K	0.0
Sequence	1 pulse
PW01	11u
PW02	
PW03	

ppm

Compound 171

File created:
Thursday, 31 October 2002
11:51 AM

Nucleus	C13
Points 1D	16384
Acq. Points	16384
Dwell 1D	61u
SW +/-	8196.7
FILTER	8150
Acq. Time	999.424m
Scans 1D	256
Dummy scan	0
Scan Count	256
Last Delay	2s
Obs Freq	68.0475401
RCVR gain	32
spin rate	5
Sequence	1 pulse-Dec
PW01	3.75u
LB 1D	2.00
Filename	BK2/18 bis C13
Date	31/10/02

Compound 171

File created:
Thursday, 31 October 2002
11:54 AM