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A NOVEL SYNTHESIS OF LORATADINE
AND
STUDIES ON STOBBE-LIKE CONDENSATION REACTIONS

by

Matthias Christoph Eichler

A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy

July 2006

Trinity College Dublin

Declaration

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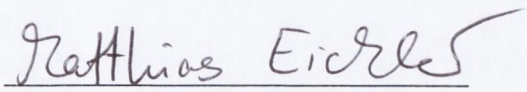


Matthias Eichler

Summary

Loratadine is one of the best-selling, non-sedative antihistamines worldwide. Numerous papers have been published in academic and patent literature focussing on improvements or alternatives to the original synthesis of Loratadine and its precursors. The most significant of these synthetic approaches, including the original synthesis of the drug, are outlined in Chapter 1. This is followed by the presentation of a novel strategy to access an important Loratadine precursor, 3-[2'-(*m*-chlorophenyl)ethyl]picolinic acid, from inexpensive starting materials. The synthesis of this precursor was the first project of this Thesis.

Chapter 1 also contains the description of a Horner-Emmons reaction between deprotonated diethyl (2-carbomethoxy)benzylphosphonate and 2-furaldehyde, a reaction that had been carried out previously. According to the author, this experiment yielded the expected Horner-Emmons alkene as the minor and a novel vinylphosphonate as the major product. The formation of this unsaturated phosphonate was believed to proceed *via* a Stobbe-like mechanism, but at the time this reaction was not much further investigated. However, this side-reaction was of interest in connection with the first project of this Thesis, involving a Horner-Emmons reaction between 3-formyl-2-carbomethoxypyridine and the anion of diethyl 3-chlorobenzylphosphonate, in which a similar side-reaction might have prevented the formation of the expected stilbazole. Also, vinylphosphonates are useful building blocks in organic synthesis and this type of reaction might offer a new route towards these compounds.

In the first part of Chapter 2, a brief historical overview of ozonolyses of quinolines is presented, a reaction which was considered the crucial step in the synthesis of 3-[2'-(*m*-chlorophenyl)ethyl]picolinic acid. This overview is followed by a detailed discussion describing how this important Loratadine precursor was accessed *via* a novel, cost-efficient and environmentally benign synthetic pathway.

The synthesis of novel vinylphosphonates from the anions of diethyl (2-carboalkoxy)benzylphosphonates and simple aldehydes and ketones, for example, benzaldehyde or acetophenone, was the second project of this Thesis and is discussed in Chapter 3. The proposed mechanism which leads to the unsaturated phosphonates is reminiscent of the classical Stobbe reaction and involves the formation of intermediate lactones. This mechanism would also explain the unsuccessful outcome of a Horner-Emmons reaction carried out during the project described in Chapter 2.

Chapter 4 is an extension of the work described in Chapter 3. It was considered that Stobbe-like condensations using sulfones analogous to diethyl (2-carboethoxy)-benzylphosphonate, *e.g.* ethyl 2-{[(4-methylphenyl)sulfonyl]methyl}benzoate, might give facile access to vinylsulfones. The conditions that were used in these reactions were almost identical to those that were used in the experiments described in Chapter 3.

Acknowledgements

Firstly, I would like to thank my supervisor Prof. David H. Grayson for invaluable discussions and his help and guidance during the course of this work.

My sincerest thanks go out to Prof. John Corish for the use of the facilities at Trinity College and to the technical staff, in particular to "Mr. NMR" Dr. John O'Brien. Financial support came from Trinity College Dublin, for which I am very grateful indeed.

Over the last five years I had the pleasure and honour to meet and get to know a huge number of great friends and colleagues: Guillaume, Cécile, Samuel, Úna, Jérôme, Gillian, Phil, Dave, Elnaz, Breege, Marco, Ruaidri, Isabel, Anne, Frank, Alessandra, Valentine, Carole, Richard, Stephan from France, Stephan from the US, Anthony, Damien, Trinidad, Jose, Shane, Adriaan, Igor, Delphine, Alberto, James and many more. Thanks to all of you for a wonderful and very enjoyable time in Ireland.

I am very glad to see that even while there is a lot of water between us, the "BecksBierBoys", *i.e.* Christian, Paco, Christopher, Daniel, Sladjan, Tim, Mike and Holger, still stay in contact with each other and I am very much looking forward to the next time we meet.

A big thank you to my brothers Christian, Felix and Philipp and my sister Susanne. I really miss you and I hope we will see each other more often in the near future.

Last but not least I would like to thank my parents Christa and Richard which is not an easy thing to do: the financial and mental support you gave me during the course of this work, and indeed throughout my whole life, deserves a whole thesis full of "thank you"s. Although appropriate, it would be quite a boring read, so instead I am going to use the wonderful format functions to try to express my sincerest gratitude:

T H A N K Y O U !

Table of contents

List of Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
AIBN	2,2'-azobisisobutyronitrile
app.	apparent
Br	broad
b. p.	boiling point
Bu	*n*-butyl
***s*-Bu**	*sec*-butyl
***t*-Bu**	*tert*-butyl
cat.	catalyst
CNS	central nervous system
D	doublet
DBU	1,8-Diazabyciclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEPT	distortion enhancement by polarisation transfer
DMF	*N*,*N*'-dimethylformamide
DMSO	dimethylsulfoxide
dt	double triplet
Et	ethyl
FDA	Food and Drug Administration
FPT	farnesyl protein transferase
HMBC	heteronuclear multiple-bond correlation

HRMS	high resolution mass spectroscopy
IgE	immunoglobulin E
IR	infrared
J	scalar coupling constant
m	multiplet
m	meta
m. p.	melting point
m/z	mass per unit charge
Me	methyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
n.O.e.	nuclear Overhauser effect
o	ortho
OTC	over-the-counter
p	para
PAF	platelet activating factor
PAR	perennial allergic rhinitis
Ph	phenyl
ppm	parts per million
***i*-Pr**	isopropyl
Pyr	pyridine
q	quartet

r. t.	room temperature
s	singlet
SAR	seasonal allergic rhinitis
t	triplet
THF	tetrahydrofuran
TOCSY	total correlation spectroscopy

CHAPTER 1:

Introduction

1.1 The allergic reaction

The allergic reaction is a complex process, which involves the interaction of a variety of cells, proteins and other biological mediators. The process starts with the sensitisation of the body towards a specific allergen which, in theory, can be any substance in our environment. The most common allergens, however, are proteins of animal or vegetable origin, for example pollen and animal dander. Upon intrusion and detection of these "foreign" substances, B-cells start with the production of antigen-specific immunoglobulin E (IgE). These IgE-antibodies attach themselves onto the surface of basophils, a cell type which is present in the blood, and mast cells, which are expressed in all tissues that have contact to the environment, for example in the mucosa of the digestive tract and lungs, and in the skin, nose and mouth (**Figure 1.1**).

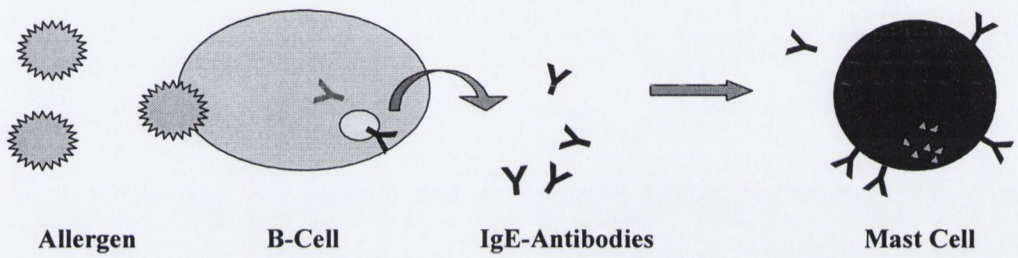


Figure 1.1: Production of antibodies and "priming" of mast cells.

The next time the antigen is inhaled or ingested it soon comes in contact with these "primed" cells. When this happens, two of the IgE-antibodies attached to the cells surface bind to specific sites of the allergen (**Figure 1.2**).

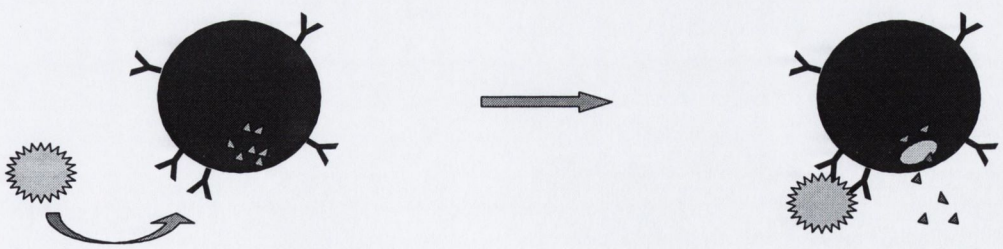
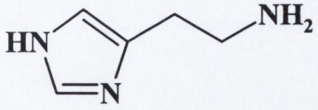


Figure 1.2: Binding of an allergen molecule to a mast cell followed by degranulation of the cell.

This cross-linking of two antibodies triggers the degranulation of the cell, *i.e.* the release of over thirty chemical mediators, including histamine **1**, into the surrounding tissues. The binding of these messenger molecules to specific receptor sites then causes the typical symptoms of the allergic reaction and inflammation.



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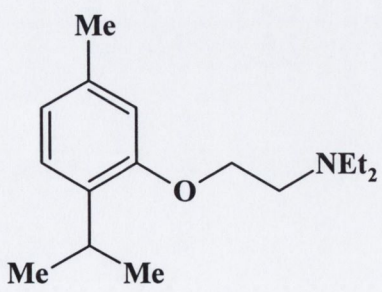
1.2 Histamine, H receptors and antihistamines

Shortly after its first synthesis in 1907[1] histamine **1** was found in mammalian tissues. Initial pharmacological studies were carried out by Dale and Laidlaw[2] in 1910, and several years later histamine **1** was identified[3] as a major pathogenic mediator of allergic disorders. In the human body histamine **1** is produced and stored in mast cells of peripheral tissues, in basophils and in specific neurons in the central nervous system (CNS). One of the first histamine receptor antagonists, thymoxyethyldiethylamine (*F929*) **2**, was synthesised by Einhorn and Rothlauf[4] in 1911. In studies described by Bovet and Staub,[5] this compound protected guinea pigs against lethal doses of histamine **1**. Another breakthrough was made five years later, when Halpern[6] and other researchers discovered phenbenzamine **3**, one of the first antihistamines which were successfully used in humans. In the next couple of decades an impressive number of histamine antagonists were developed, however, even potent substances like mepyramine **4** showed a lack of inhibiting all histamine-induced effects, for example at the heart and the stomach.



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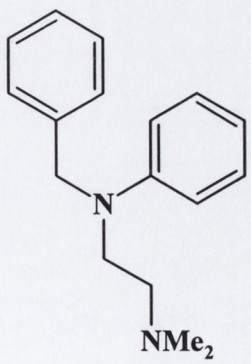

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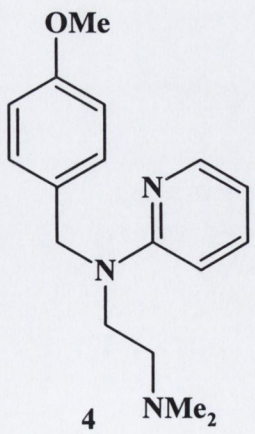
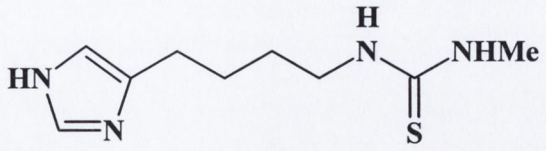


4

As a consequence, in 1966 Ash and Schild[7] postulated the existence of at least two subtypes of histamine receptors. This hypothesis was substantiated when Black and co-workers[8] synthesised new compounds, including burimamide **5**, which inhibited allergic disorders that could not be antagonised with existing antihistamines.



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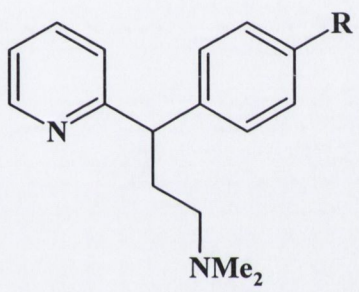
To the present day, four antihistamine receptor subtypes have been identified. The H_1 receptors are expressed in most smooth muscle cells of peripheral tissues, in sensory nerves, in the heart and in the CNS. Common allergic disorders, such as skin irritation, itching, sneezing and nasal secretion, are triggered by the action of histamine **1** on H_1 receptors. Blocking this receptor subtype with suitable antagonists is one of the most important therapeutical strategies in the treatment of seasonal and perennial allergic rhinitis (SAR/PAR).

Second class receptors (H_2) are present in the gastric mucosa, heart, uterus, lung and CNS. Binding of histamine **1** to the H_2 receptors in the stomach increases gastric acid secretion and thus, H_2 receptor antagonists are widely used in the treatment of peptic ulcers and other gastrointestinal-related diseases.[9] Histamine **1** also functions as a neurotransmitter. In 1983 Arrang *et al.* demonstrated[10] the existence of pre-synaptic H_3 receptors pharmacologically, but it was not until 1999 before their molecular structure was identified.[11] This receptor subtype is predominantly located in the brain, CNS and peripheral nervous system. It regulates the synthesis and release of histamine itself, and also that of other neurotransmitters, for example dopamine, noradrenaline and serotonine.

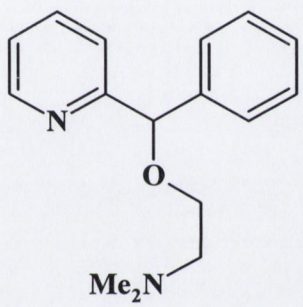
Although very different in their expression in the body, H_3 and H_4 receptors show similarities in structure and pharmacology. The latter receptor subtype is present, for example, in bone marrow, spleen and blood cells and is believed to be "an interesting therapeutic target for the regulation of immune function."[12]

1.3 First- and second generation antihistamines

The discovery of the H_1 receptor antagonist *F929* **2** marked the beginning of the first generation of antihistamines, which includes well-known drugs, such as *Chlor-tripolon*® (chlorpheniramine **6**), *Dimetane*® (brompheniramine **7**) and *Benadryl*® (diphenhydramine **8**). A lot of these compounds have proven their effectiveness and some are still available as inexpensive over-the-counter (OTC) drugs. However, all first generation antihistamines have a serious disadvantage by definition: due to high lipophilicity and rather small molecular weight they easily penetrate the CNS and then bind to H_1 receptors in the brain, which causes marked sedation and impairment of psychomotor performance. Also, some of the early antihistamines exhibit poor receptor selectivity and their binding to muscarinic and other receptors results in additional, mostly undesirable, side-effects.[12,13]



6 **R = Cl**
7 **R = Br**



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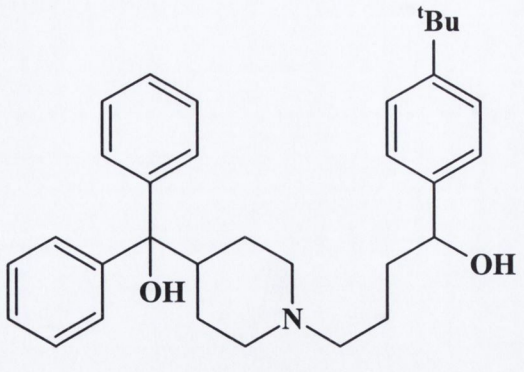
The search for non-sedating antihistamines was pursued by several companies, initially, however, with little success. After decades of fruitless research the question was raised if "a non-sedating antihistamine was maybe a contradiction in terms".[14] In the early seventies, workers from Richardson-Merrell reported[14,15] on the development and testing of another potential drug candidate, and this compound, terfenadine **9**, showed indeed no or only little sedation at therapeutic doses. *Seldane*®, the official brand name of the drug, was given approval by the Food and Drug Administration (FDA) in the US in 1985 and was subsequently marketed as the first non-drowsiness antihistamine. In 1988, *Seldane*® was joined by *Hismanal*® (astemizole **10**), which is also a so-called second generation, *i.e.* a non-sedating, antihistamine.



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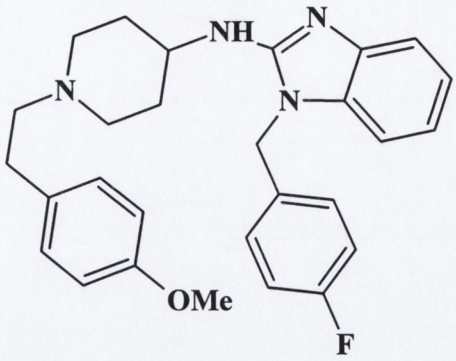

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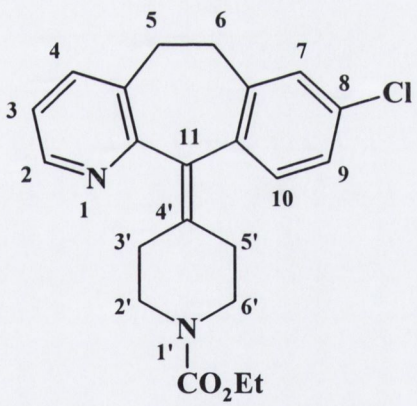
1.4 History of Loratadine 11

Another competitor in the race of developing non-sedating histamine antagonists was Schering, a company which at the time already had a considerable antihistamine business. Their candidate was Loratadine **11**, which is the common name for ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate. It is closely related to azatadine **12**, which was first described in the patent literature in 1964 by Villani and co-workers.[16]



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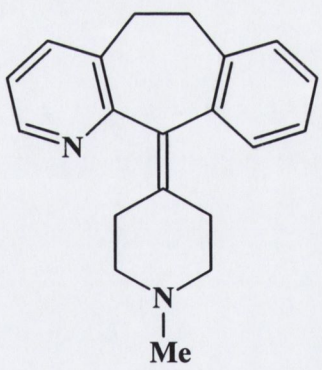

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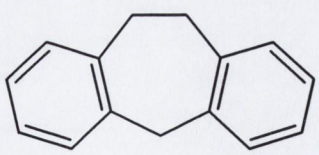


13

By that time it was already known[17] that many derivatives of 5,6-dihydro-11*H*-dibenzo[*a*,*d*]cycloheptene **13** had pronounced biological activities. Pharmaceutical tests on these compounds concentrated mostly on their antidepressant and tranquilising effects but their antihistaminic potency was soon discovered.

Villani's group extended their investigations to compounds where one of the benzene rings was replaced by a pyridine ring.[16,18,19] The 4-aza series, due to changes in nomenclature now 1-aza series, included the most potent derivatives and thus synthetic efforts were concentrated in this area. Screening results from more than sixty derivatives revealed that the dimaleate of azatadine **12**, *i.e.* 6,11-dihydro-11-(-methyl-4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine, exhibited the highest antihistaminic and antianaphylactic potency.[19] Azatadine **12** was introduced to the market in 1973 and sold under the name *Optimine*®. Like many other antihistamines before, this compound was expected[14] to have no sedative effects. This assumption was based on clinical trials with several animal species, however, when the drug was tested in humans, significant sedation was observed.

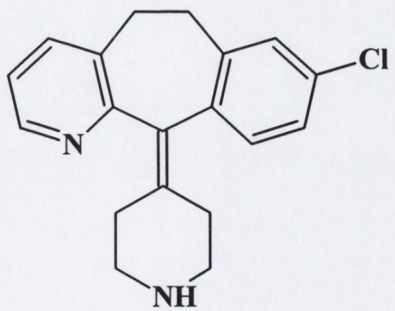
Loratadine **11** itself was not mentioned in the literature until 1981 when another patent[20] was published by the Schering corporation. In preliminary tests Loratadine **11** showed at least the same antihistaminic potency as the standard drugs available at that time.[21] Also, among several other benefits,[22,23] Loratadine **11** did not have significant sedative effects on animals and humans. This was explained[24] after experiments showed that Loratadine **11** exhibited high selectivity in binding to different H_1 histamine receptors. When the affinity of receptors in the lung and cortex membranes of guinea pigs towards the drug was compared, Loratadine **11** bound almost exclusively to the lung receptors, which is desired and which prevents sedation. Also, Loratadine **11** does not penetrate easily the blood-brain barrier.[24]

Loratadine **11** was patented by Schering in the US as a drug for treating allergic disorders in 1986. However, as *Seldane*® was already on the market and *Hismanal*® under review, the FDA refused to grant approval for a drug that "essentially duplicates in medical importance and therapeutic usage one or more already marketed drugs, offering little or no therapeutic gain over existing therapies."[25]

An important turning point in the eventful history of Loratadine **11** was the discovery of serious interactions between the active ingredients of *Hismanal*® and *Seldane*® and widely used antibiotics such as ketoconazole and erythromycin. Those interactions led to dangerous irregularities in heartbeat, and suddenly the FDA "started to believe that it would be beneficial to have *Claritin*®, the official brand name of Loratadine **11**, for sale."[25]

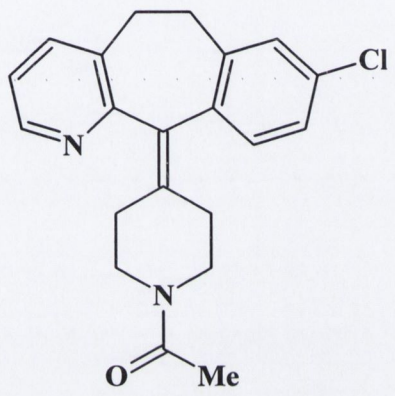
In April 1993, *Claritin*® finally hit the US-market and did so with huge impact. Soon after its introduction, and especially after the FDA had relaxed advertisement regulations in the US in 1997, the drug climbed quickly to the top of the sales charts and is now the most-profitable antihistamine of all time. In 2001, for example, global sales rose to $ 3.1-billion (US-market: $ 2.7-billion).[25] Since then, however, profits have dropped significantly which is due to switching the drug to OTC-status and due to the introduction of generic products when Loratadine patents expired at the end of 2002.

In early 2002 a successor to *Claritin*® named *Clarinex*® was introduced by Schering, and is a substance which is claimed to be even more effective than Loratadine **11**. The active component of this new drug is desloratadine **14**, which is also the major metabolite of Loratadine **11** and which can easily be derived from the latter by decarbethoxylation.[26,27]



14

In addition to their antihistaminic and antianaphylatic properties, Loratadine **11** derivatives have found even further application.[28-34] For example, the acetamide **15** is a potent platelet activating factor (PAF) antagonist[28] and the pyridine-substituted amide **16**, also referred to as Sch 56580, acts as a farnesyl protein transferase (FPT) inhibitor.[31] Like histamine **1**, PAF is a chemical mediator which is released from cells in the pathogenesis of the inflammatory and allergic response.[28-30] Inhibitors of the FPT enzyme are considered valuable compounds in cancer-therapy.[31-34] The tricycles **15** and **16** represent only a small fraction of a variety of possible drug-candidates, most of which can be prepared *via* the synthetic pathways described in the following sections.



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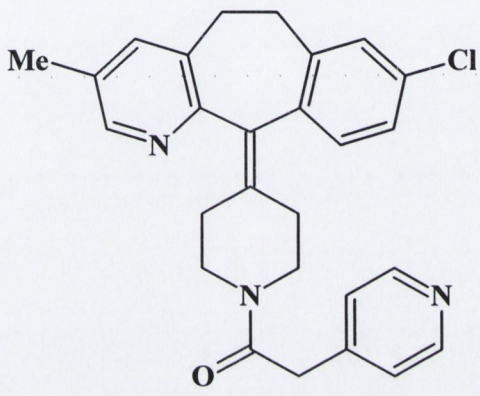

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1.5 Synthetic routes towards Loratadine 11

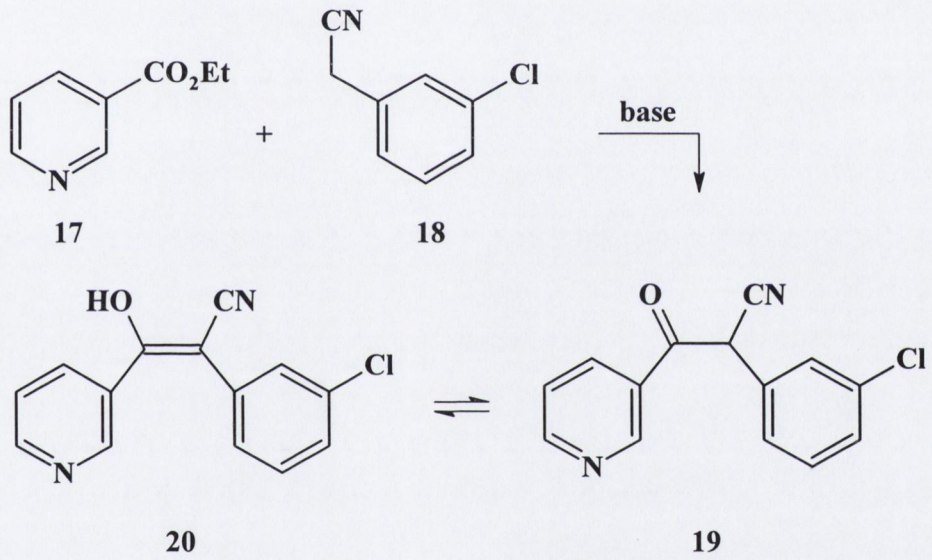
The original synthetic route (Schering route) towards Loratadine **11** is very similar to that to azatadine **12**. The synthesis[16,18-20,22] included quite a lot of steps and some of those were either expensive or not very efficient. The importance, and the pharmaceutical as well as the financial potency of Loratadine **11** was apparent, hence it is not surprising that numerous modifications and improvements to its synthesis have been reported in the last decades.[27-46] The most important synthetic routes and modifications will be presented and discussed in this chapter.

1.5.1 Synthesis of Loratadine 11 *via* the Schering route

This synthetic pathway[16,18-20,22,35] towards Loratadine **11** consists of eight steps which are outlined below.

Step 1: Condensation of ethyl nicotinate 17 with 3-chlorobenzyl cyanide 18

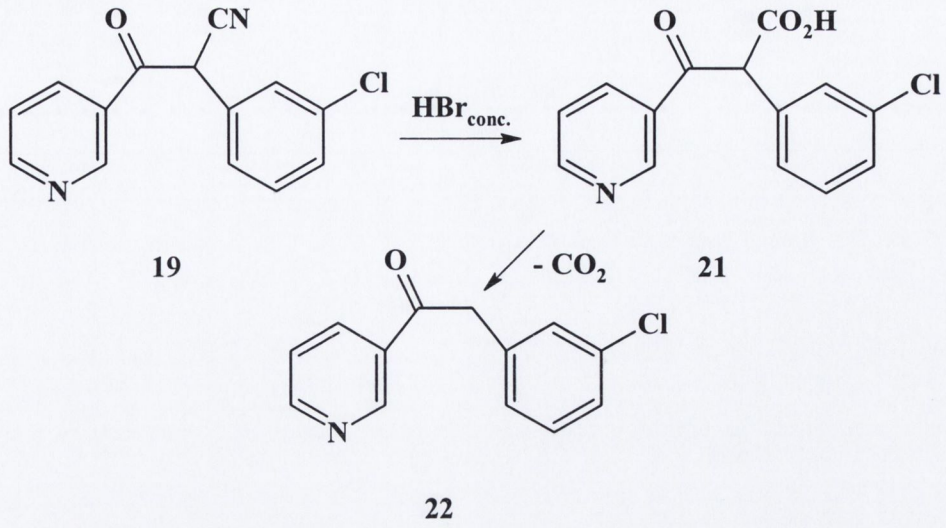
The first step in this synthesis is a Claisen-like condensation[47] between ethyl nicotinate **17** and 3-chlorobenzyl cyanide **18**. The keto-nitrile **19**, which is in equilibrium with its tautomeric form **20**, is obtained by generating the benzylic anion of **18** with base followed by nucleophilic addition to the ester **17** and subsequent loss of ethoxide ion (**Scheme 1.1**).



Scheme 1.1: Condensation of ethyl nicotinate **17** with the benzyl cyanide **18**.

Step 2: Hydrolysis and decarboxylation of the keto-nitrile 19

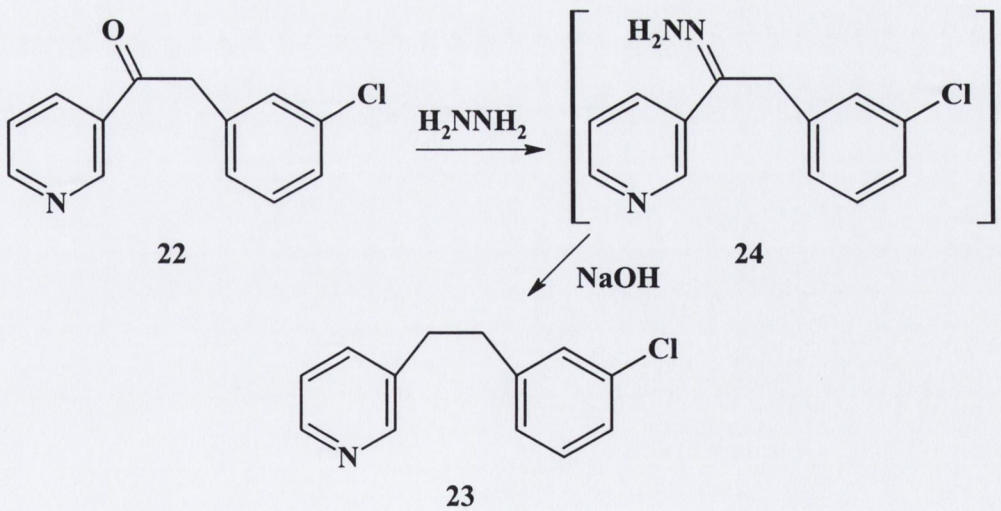
Under acidic conditions nitriles can be hydrolysed to carboxylic acids, a reaction that is also utilised in the present case. Hydrolysis of **19** gives the β-keto acid **21** which conveniently undergoes spontaneous decarboxylation to give 3-chlorobenzyl-3'-pyridylketone **22** (**Scheme 1.2**).



Scheme 1.2: Hydrolysis of the keto-nitrile **19** followed by decarboxylation of the keto-acid **21**.

Step 3: Reduction of the benzyl 3-pyridyl ketone 22

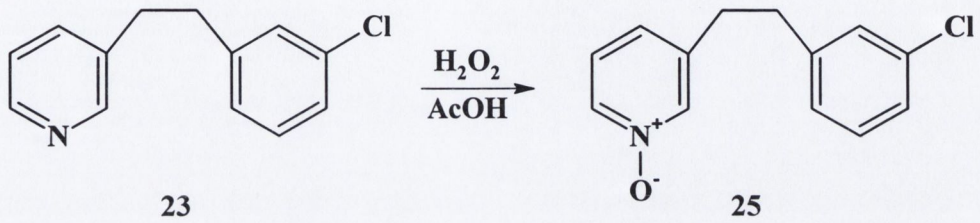
A Wolff-Kishner[48] reaction (**Scheme 1.3**) was used to reduce the ketone **22** to 3-(*m*-chlorophenethyl)pyridine **23**. Hydrazine reacts with the carbonyl group of **22** to yield the corresponding hydrazone **24** which reacts when heated *in situ* with base (NaOH) to give **23** together with nitrogen gas.



Scheme 1.3: Wolff-Kishner reduction of the ketone **22**.

Step 4: Preparation of the *N*-oxide 25

Oxidation of the pyridine nitrogen can be achieved with, for example, peroxyacids or reagents like potassium peroxymonosulfate (Oxone®). In the present case 3-(*m*-chlorophenethyl)pyridine **23** was treated with peroxyacetic acid, prepared *in situ* from acetic acid (AcOH) and hydrogen peroxide (**Scheme 1.4**).

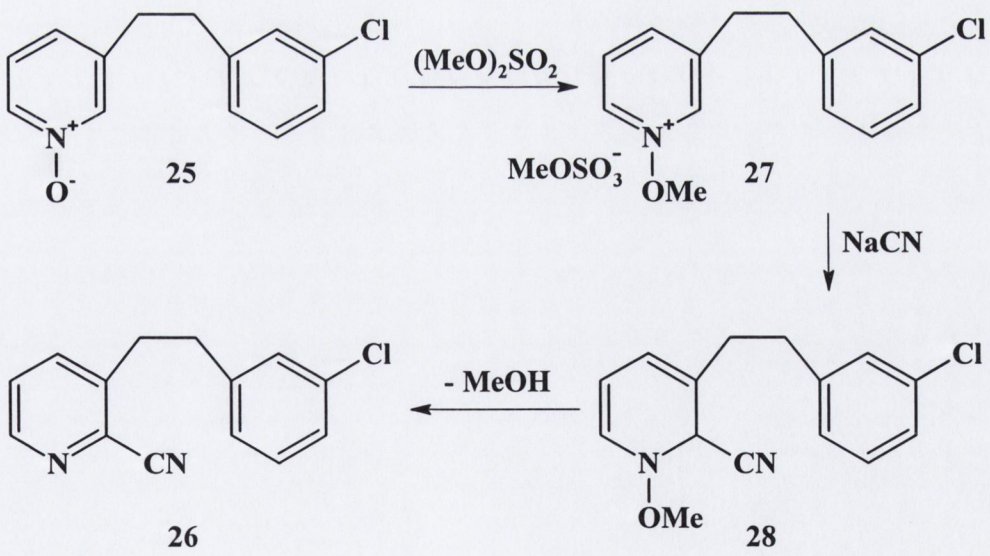


23 **25**

Scheme 1.4: Preparation of the *N*-oxide **25** using hydrogen peroxide and AcOH.

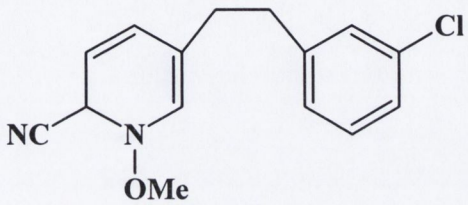
Step 5: Preparation of the nitrile 26

The Reissert reaction[49] is one of the key steps in this route and the nitrile **26** is the most important intermediate for accessing Loratadine **11**. The reaction involves two steps which can be carried out in a one-pot process (**Scheme 1.5**).

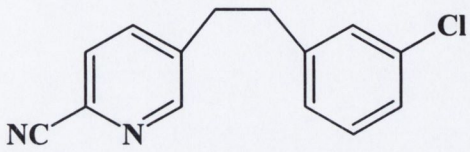


Scheme 1.5: Preparation of the nitrile **26** *via* a Reissert reaction.

First, the *N*-oxide **25** needs to be activated, *i.e.* alkylated or acylated. Methylation of **25**, for example with dimethyl sulfate, gives the intermediate **27**, which then undergoes nucleophilic attack by cyanide ion to yield the nitrile **28**. Subsequent elimination of methanol from **28** leads to the desired 2-cyanopyridine **26**. Besides the use of very toxic reagents (dimethyl sulfate, sodium cyanide), another major drawback of this process is the formation of the isomeric nitrile **29**, which further reacts to give the 6-cyano-derivative **30**.



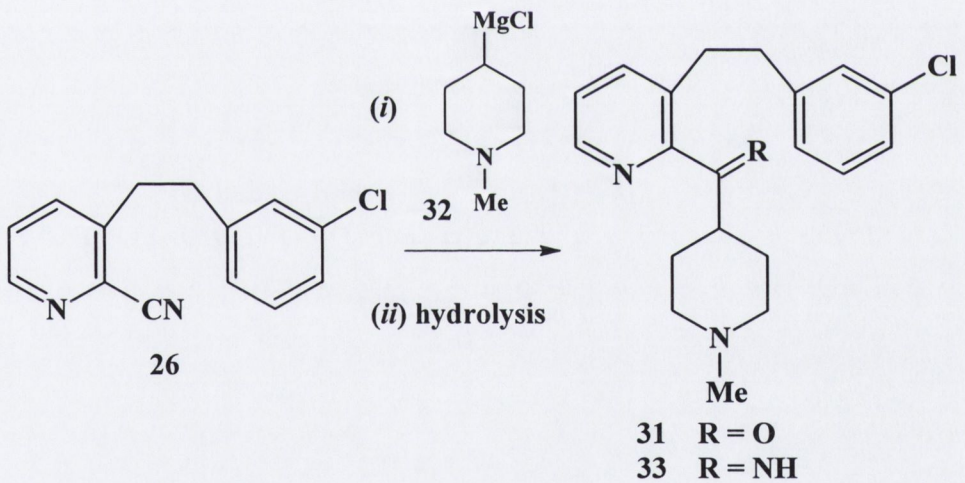
29



30

Step 6: Preparation of the piperidyl ketone 31

The piperidyl ketone **31** was obtained by a Grignard reaction as shown in **Scheme 1.6**.



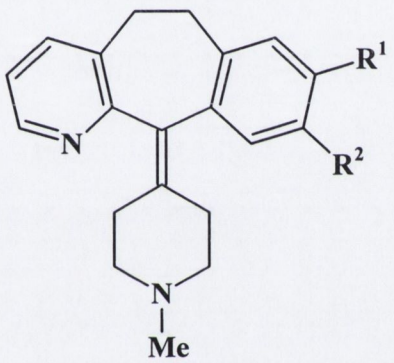
Scheme 1.6: Preparation of the piperidyl ketone **31** by Grignard reaction of **26** and subsequent hydrolysis of the imine **33**.

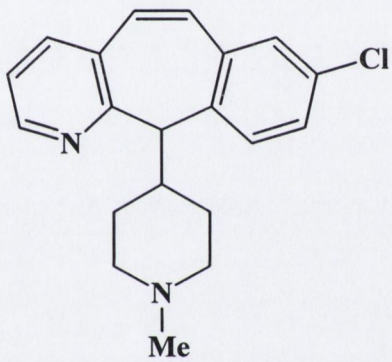
The nitrile **26** was added to the Grignard reagent **32**, prepared from 4-chloro-1-methylpiperidine and magnesium, which initially gave the imine **33**. The latter compound is readily hydrolysed with aqueous acid to yield the desired ketone **31**.

Step 7: Cyclisation of the ketone 31 to give 8-chloroazatadine 34

This cyclisation step is probably the best-investigated reaction in the entire synthesis, and multiple strategies and reagents have been applied to afford the desired tricyclic products in satisfactory yields and purities.

Polyphosphoric acid (PPA) was one of the very first reagents used in the preparation of azatadine **12**.[16a] However, when the same reaction was attempted[35a] with the chloro-derivative **31**, not only the desired tricycle **34**, but also the double bond isomer **35** was formed, and yields of **34** did not exceed 45 %. From this it was concluded that stronger acids with a Hammett acidity function[50] of less than –14 would be needed.





12 $R^1 = H, R^2 = H$
34 $R^1 = Cl, R^2 = H$
36 $R^1 = Cl, R^2 = SO_2Me$

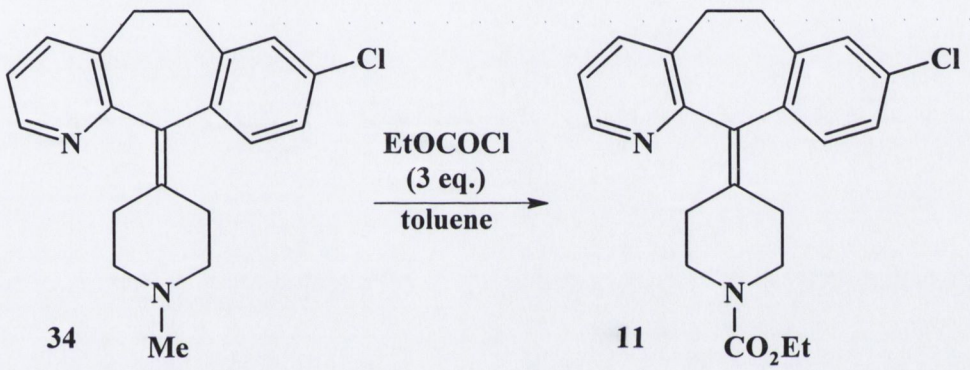
35

Reaction of **31** with a mixture of boron trifluoride and methanesulfonic acid gave **34** in high yield, but when this process was scaled up, significant amounts (>10 %) of the 9-methylsulfonyl substituted derivative **36** were found in the product mixture.[35] Cyclisation of **31** to give **34** by means of trifluoromethanesulfonic acid[35] led to good results, but the reagent is very expensive. The best reagent found for the dehydration/cyclisation step was boron trifluoride in hydrofluoric acid. The reaction was carried out at –30 °C for one hour and gave consistently more than 90 % of the theoretical yield of **34**.[35]

Optimised reaction conditions have been reported by Suri, Singh and Naim,[36] who conducted the cyclisations at much lower temperatures (-90 °C), thus increasing the yield and purity of 8-chloroazatadine **34**.

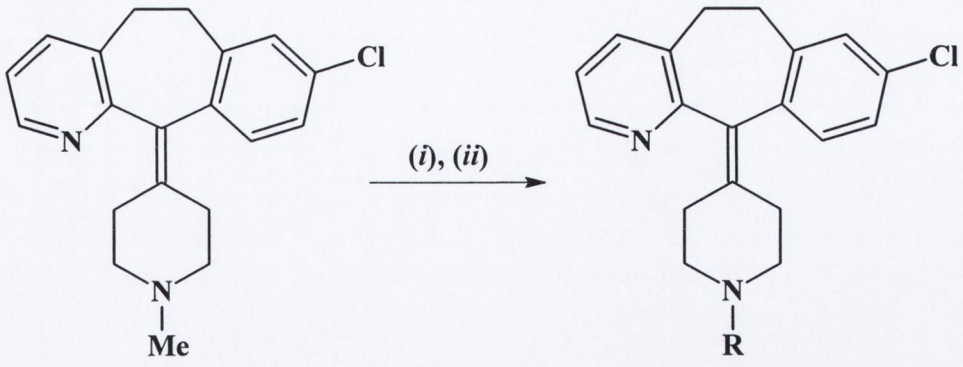
Step 8: Preparation of Loratadine 11

In the final step of this synthesis, the *N*-methyl group of the tricyclic piperidine compound **34** must be replaced with a carboethoxy group. This was done[22] by heating **34** with a three-fold molar excess of ethyl chloroformate (EtOCOCl) in benzene or toluene to yield Loratadine **11** directly (**Scheme 1.7**).



Scheme 1.7: Preparation of Loratadine **11** from the *N*-methyl piperidine **34**.

A second method[26] for this transformation utilised a von Braun reaction[51] in which **34** was converted into the nitrile **37** by treatment with cyanogen bromide in benzene (**Scheme 1.8**). Hydrolysis of the nitrile **37** with hydrochloric acid then yielded the carbamic acid derivative **38** which underwent spontaneous decarboxylation to give desloratadine **14** (**Scheme 1.8**). From this compound **14** a variety of other derivatives can be synthesised, which is the only real advantage of this route. For example, when **14** is treated with ethyl chloroformate the reaction yields Loratadine **11**.



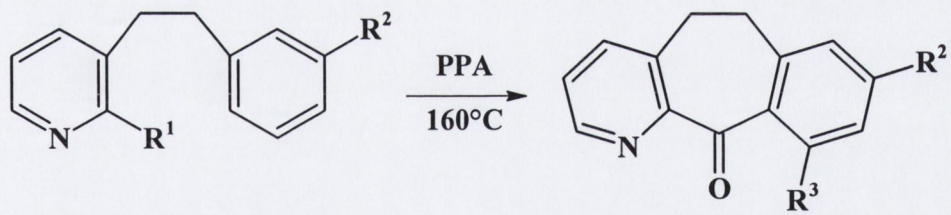
34

37 R = CN
38 R = CO_2H
14 R = H

Scheme 1.8: Preparation of desloratadine **14** from 8-chloroazatadine **34**. Reaction conditions: (*i*) BrCN/benzene (*ii*) hydrolysis with HCl_{aq} and spontaneous decarboxylation.

1.5.2 Synthesis of Loratadine 11 *via* the alternative Schering route

An alternative route to Loratadine **11** can already be found within the first published synthesis[16] of azatadine **12**. There, 2-cyano-3-phenethylpyridine **39** is cyclised using a ten-fold weight excess of PPA at 160 °C to give the ketone **40** (**Scheme 1.9**). The same compound **40** is obtained when, prior to ring-closure, the nitrile **39** is converted into the carboxylic acid **41** by hydrolysis.

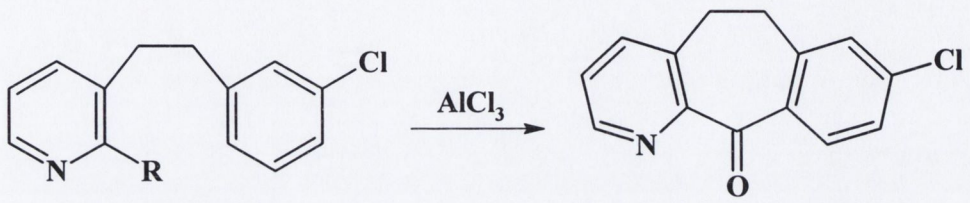


39 R^1 = CN; R^2 = H
41 R^1 = CO_2H; R^2 = H
26 R^1 = CN; R^2 = Cl

40 R^2 = H; R^3 = H
42 R^2 = Cl; R^3 = H
43 R^2 = H; R^3 = Cl

Scheme 1.9: Cyclisation of the acid **41** and the nitriles **39** and **26** using PPA.

However, this procedure is not very useful when it is applied[18] to the 3-chlorophenyl derivative **26**. Besides the low yield (~45 %) of the 8-chlorotricyclic ketone **42**, an isomer, identified as the 10-chloro compound **43**, is formed which is a serious disadvantage of this route. An improvement to this method was reported[18] in the same paper: the acid chloride **44** was prepared from the carboxylic acid **45** and cyclisation was then carried out under Friedel-Crafts conditions (**Scheme 1.10**). In this case the desired isomer **42** was obtained exclusively in 77 % yield.

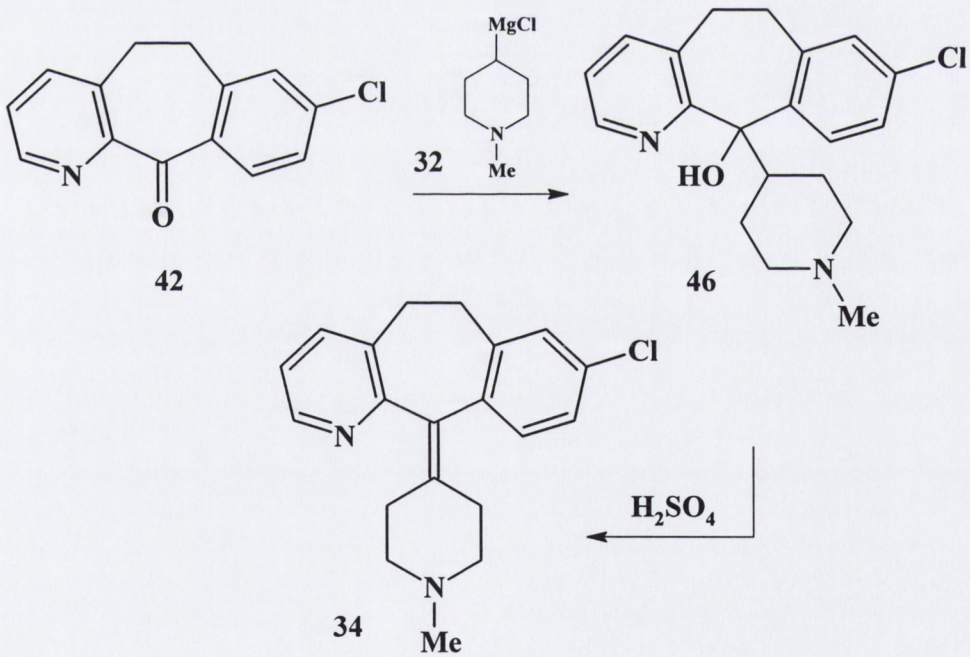


44 R = COCl
45 R = CO_2H

42 (77 %)

Scheme 1.10: Cyclisation of the acid chloride **44** under Friedel-Crafts conditions.

The ketone **42** was then reacted with the Grignard reagent **32** derived from 4-chloro-1-methylpiperidine to give the tertiary alcohol **46** (**Scheme 1.11**).



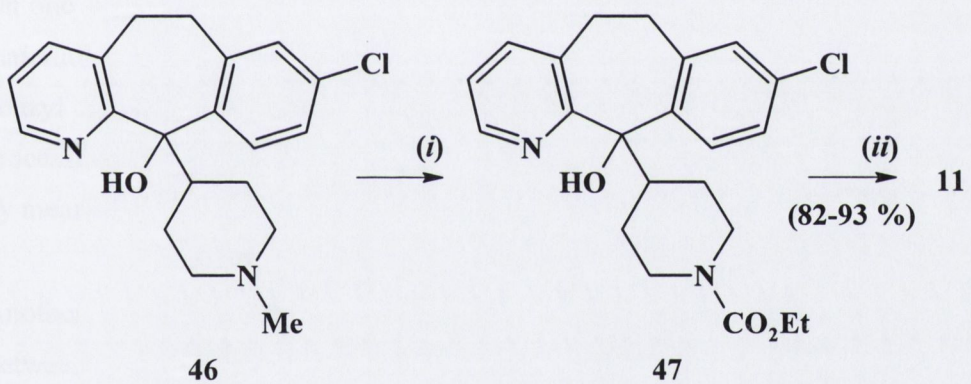
42 **46** **34**

Scheme 1.11: Preparation of 8-chloroazatadine **34** by Grignard reaction of **42** and subsequent dehydration of the tertiary carbinol **46**.

Dehydration of the carbinol **46** was accomplished by treating it with 85 % sulfuric acid at 105 °C which leads to 8-chloroazatadine **34** (**Scheme 1.11**). Loratadine **11** was then obtained from **34** by treatment with ethyl chloroformate (*cf.* **Scheme 1.7, p15**).

1.5.3 Synthesis of Loratadine 11 *via* the Inke route

The preparation of the carbinol **46** is also the point at which the Inke route[37] sets in. First, the alcohol **46** is reacted with ethyl chloroformate in the presence of triethylamine to yield the *N*-carboethoxy derivative **47**. Loratadine **11** is then obtained by dehydration of **47** with strong acids. Good yields are obtained when 93 % sulfuric acid is used. Stirring the mixture for 20 h at 0 °C affords 82 % of **11**. When **47** is reacted with methanesulfonic acid at 150 °C for 1 h, 84 % of the theoretical yield of **11** is obtained (**Scheme 1.12**).

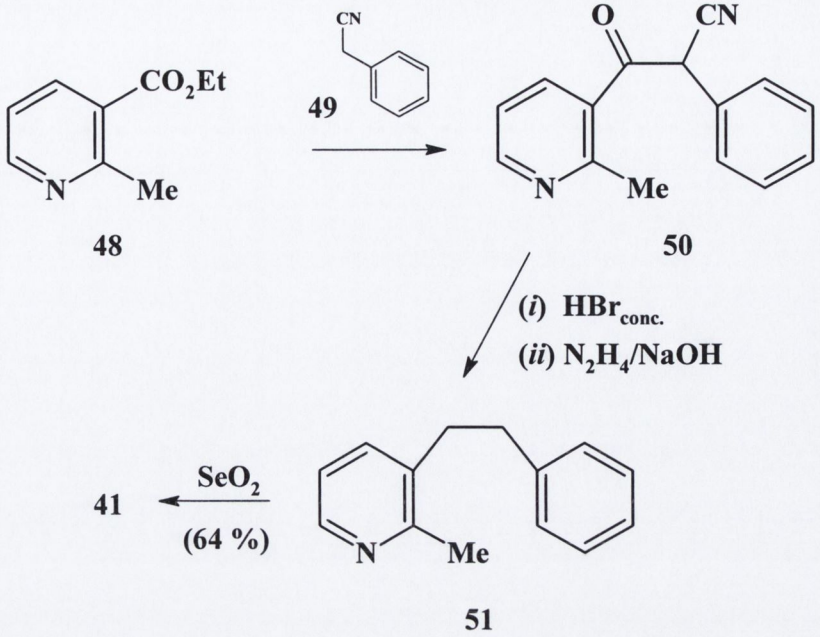


46 **47**

Scheme 1.12: Synthesis of Loratadine **11** *via* the Inke route.
Reaction conditions: (*i*) EtOCOCl/Et_3N (*ii*) strong acid, *e.g.* conc. H_2SO_4.

1.5.4 Modifications to the standard routes

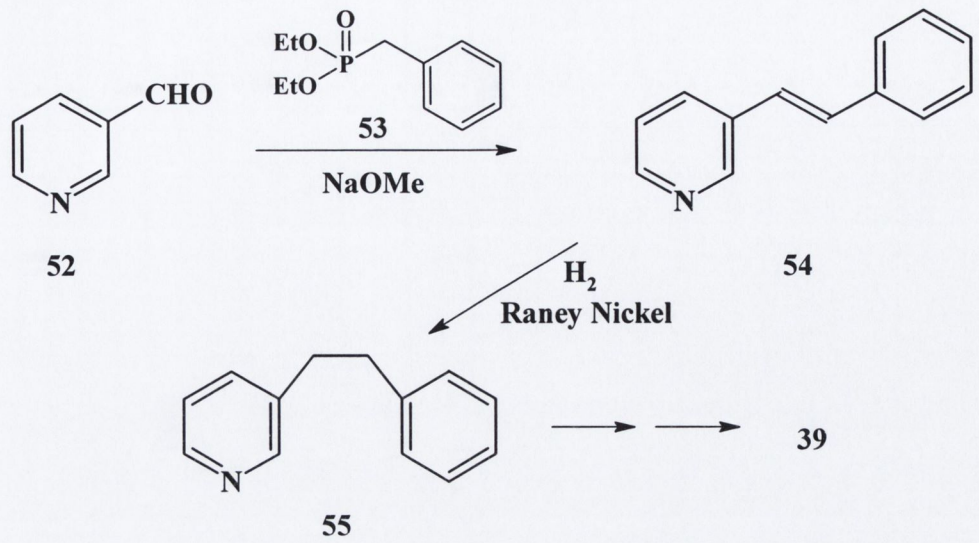
Modifications to the preparation of the nitrile **26**, the non-chlorinated nitrile **39** and their corresponding carboxylic acids **41** and **45**, respectively, were already described in one of the earlier papers by Villani *et al.*[18]



Scheme 1.13: Alternative preparation of the acid **41**.

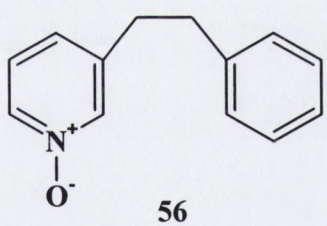
On one occasion, for example ethyl 2-methylnicotinate **48** was used as the starting material. As it is described in **Section 1.5.1 (p10)**, the ester **48** was reacted with benzyl cyanide **49** to yield the 2-methyl-substituted keto-nitrile **50**. Further processing of **50** yielded 2-methyl-3-phenethylpyridine **51**. The latter was oxidised by means of selenium dioxide to give the acid **41**, in 64 % yield (**Scheme 1.13**).

Another preparation[18] of the nitrile **39** starting with a Horner-Emmons reaction between 3-pyridinealdehyde **52** and diethyl benzylphosphonate **53** was also accomplished by Villani's group. The latter reaction initially gave the *trans*-stilbazole **54** in excellent yield. The vinyl group of **54** was catalytically hydrogenated to afford 3-phenethylpyridine **55**, which was then subjected to *N*-oxidation followed by a Reissert reaction to yield the nitrile **39** (**Scheme 1.14**). The routes depicted in **Scheme 1.13** and **1.14** were not attempted with the 3-chloro-substituted derivatives of the nitrile **18** and the phosphonate **53**, but it can be assumed that results would have been similar to those described here.



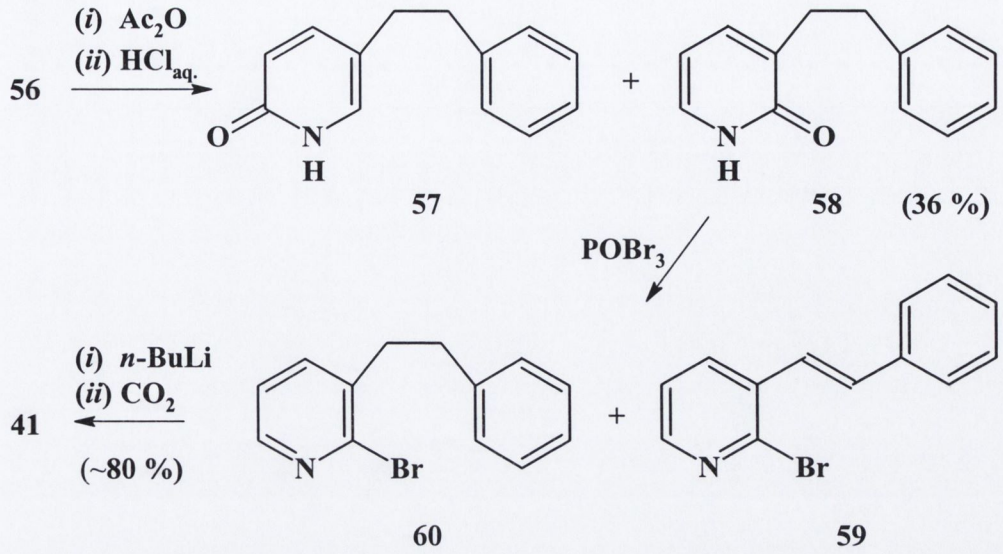
Scheme 1.14: Synthetic route towards the nitrile **39** from 3-formylpyridine **52**.

Efficient and inexpensive introduction of the cyano- or carboxylic acid group in the 2-position of the pyridine ring is undoubtedly not an easy task and the attempts to achieve this target have shown some more or less serious disadvantages so far. Yet another preparation was described by Villani *et al.*[18] where the *N*-oxide **56** of 3-phenethylpyridine was refluxed with acetic anhydride and the product then hydrolysed with concentrated hydrochloric acid to give the two isomeric pyridones **57** and **58**.



56

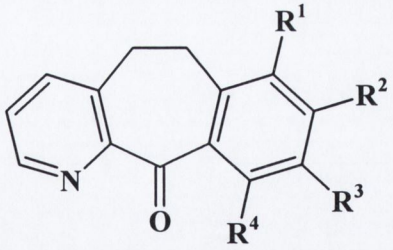
In the next step, the isomer **58**, which was obtained in 36 % yield, was reacted with phosphorus oxybromide to give two major products. One of these was identified as the 2-bromo-*trans*-3-stilbazole **59**, and the other as the desired 2-bromo-3-phenethylpyridine **60**. The latter compound was metalated with one equivalent of *n*-butyllithium (*n*-BuLi) and the derived organolithium was carboxylated using solid carbon dioxide to give the carboxylic acid **41** in ~80 % yield (**Scheme 1.15**).



Scheme 1.15: Alternative preparation of the acid **41** starting from the *N*-oxide **56**.

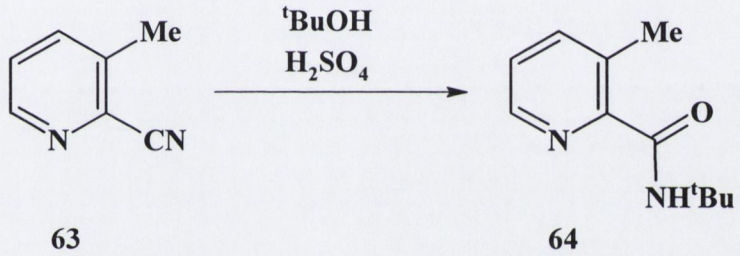
As before, this process was not used to prepare the 3-chloro derivative **25** of the *N*-oxide **56**, but similar results can be expected. Despite the good yield in the last step, this route (**Scheme 1.15**) is obviously not very useful. Firstly, it requires more steps than the synthesis of the chloro-substituted nitrile **26** *via* the Reissert reaction, and secondly, the desired intermediate products are obtained in low yields and they are accompanied by large amounts of by-products, such as the isomeric pyridone **57** and the stilbazole **59**. In addition, the use of *n*-butyllithium makes preparation of **41** *via* this route quite expensive.

It was pointed out above that cyclisation of the nitrile **26** or the carboxylic acid **45** using polyphosphoric acid yielded a mixture of two isomers, the desired 8-chloro-azaketone **42** and the by-product 10-chloroazaketone **43**. An alternative experiment was carried out by Villani *et al.*[18] in which direct chlorination of the unsubstituted ketone **40** was attempted. However, reacting the latter compound with an equimolar amount of chlorine and silver sulfate in the presence of sulfuric acid yielded only the 7- and 9-chloroketones **61** and **62**, which were isolated in low yields.



40 $R^1 = R^2 = R^3 = R_4 = H$
42 $R^1 = R^3 = R^4 = H$; $R^2 = Cl$
43 $R^1 = R^2 = R^3 = H$; $R^4 = Cl$
61 $R^2 = R^3 = R^4 = H$; $R^1 = Cl$
62 $R^1 = R^2 = R^4 = H$; $R^3 = Cl$

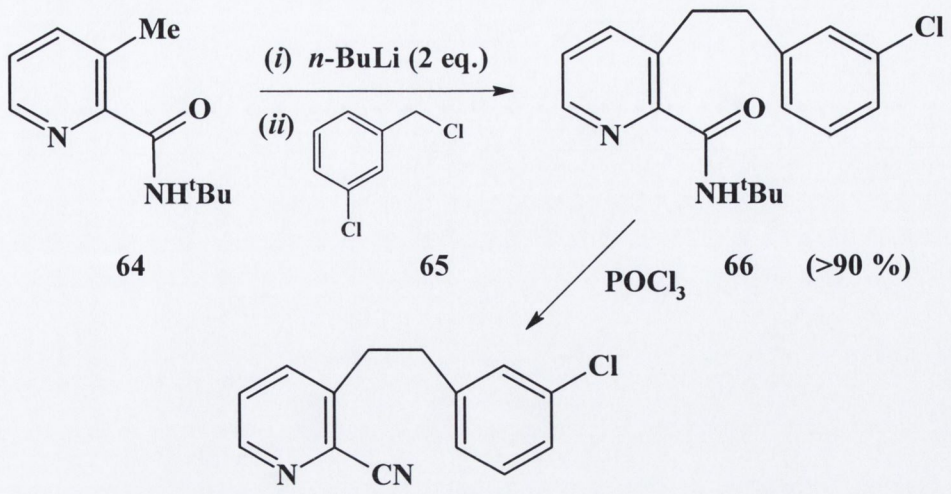
Schumacher *et al.*[35] have shown a different synthetic approach towards the nitrile **26**. In this process the *tert*-butylamide **64**, prepared from 2-cyano-3-methyl-pyridine **63** in a Ritter[52] reaction (**Scheme 1.16**), was lithiated at the 3-methyl group and then alkylated with 3-chlorobenzyl chloride **65**.



63 **64**

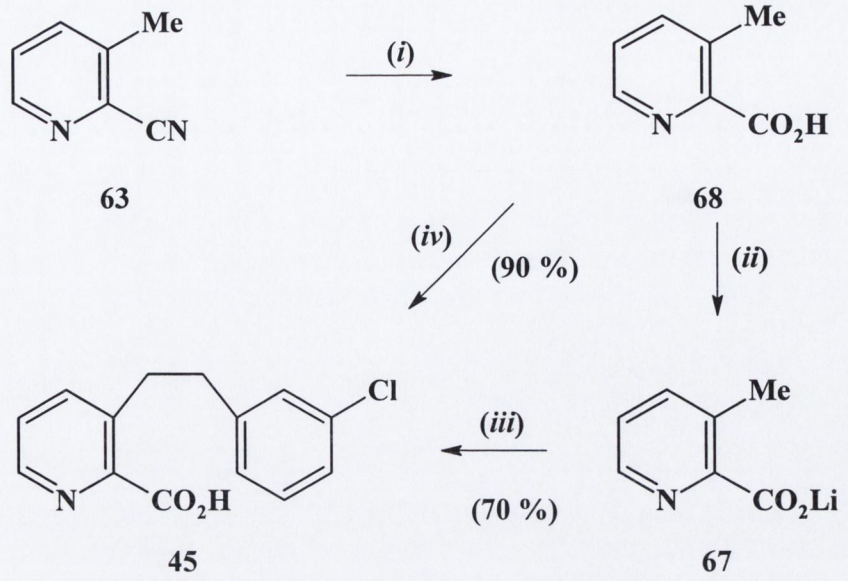
Scheme 1.16: Ritter reaction of 2-cyano-3-methylpyridine **63** to give the amide **64**.

The resulting amide **66** was refluxed in an excess of phosphorus oxychloride to yield the nitrile **26** by "dehydration" (**Scheme 1.17**). In every single step the reported yields exceeded 90 %. However, this is a costly process as two equivalents of *n*-BuLi are required and some double alkylation of **64** occurs. The starting material, nitrile **63**, is also very expensive and not easily accessible.



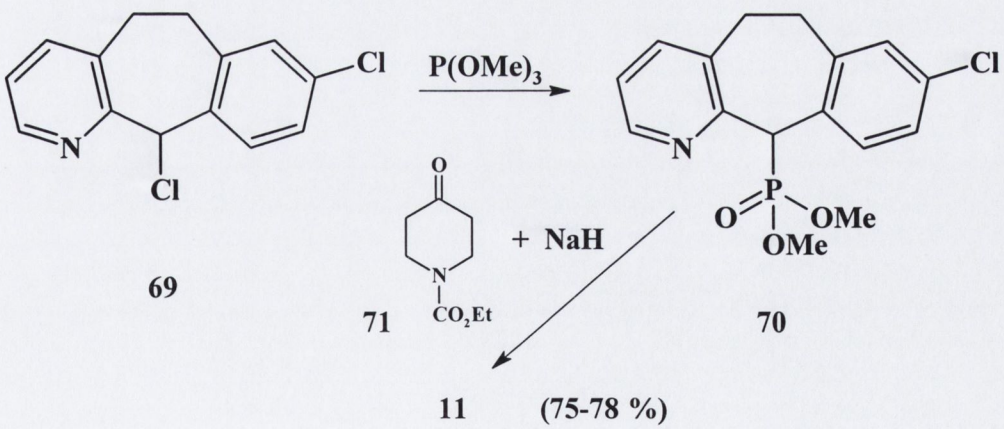
Scheme 1.17: Alternative synthesis of the nitrile **26** according to the Schumacher route.

The costly and hazardous process of connecting the pyridine and benzene ring *via* the Schumacher route, led to further investigations of this reaction. For example, Schickaneder *et al.*[38] attempted successfully the alkylation of the lithium salt **67** of 3-methylpicolinic acid **68** at temperatures between –15 and 30 °C. Using the method shown in **Scheme 1.18**, the required amount of expensive *n*-butyllithium could be reduced to one molar equivalent (*iii*) and the experiment could also be conducted at more convenient temperatures. The yield of this reaction was 70 %. Even better results have been achieved when the authors attempted to synthesise the diarylethane **45** from the acid **68** directly (*iv*). Under very mild conditions the target compound **45** was obtained in 90 % of the theoretical yield. However, deprotonation of the carboxylic acid function and lithiation of the methyl group of **68** required two moles of base. Additionally, it must be considered that the acid **68** was again prepared from the cyano-pyridine **63** which contributes largely to the overall cost of this synthetic route.



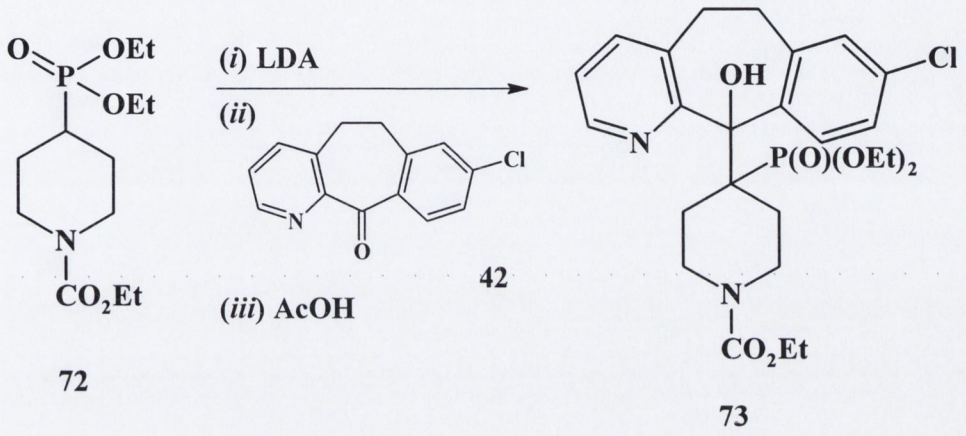
Scheme 1.18: Synthesis of the acid **45** *via* the picolinic acid **68**. Reaction conditions: (*i*) KOH/H_2O, AcOH (*ii*) LiOH/H_2O (*iii*) *n*-BuLi/THF/3-chlorobenzyl chloride **65** (*iv*) *n*-BuLi (2 eq.)/THF/3-chlorobenzyl chloride **65**.

A process published in the Spanish patent literature[39] involves the preparation of Loratadine **11** from the dichlorodihydrobenzocycloheptapyridine **69**. Almost quantitative yields were obtained when compound **69** was converted into the dimethyl phosphonate derivative **70** by means of an Arbuzov-reaction. Depending on the solvent used, Loratadine **11** was obtained from Horner-Emmons reactions of the anion of **70** with *N*-(ethoxycarbonyl)-4-piperidone **71** in THF (78 %), benzene (75 %) and toluene (76 %), respectively (**Scheme 1.19**).



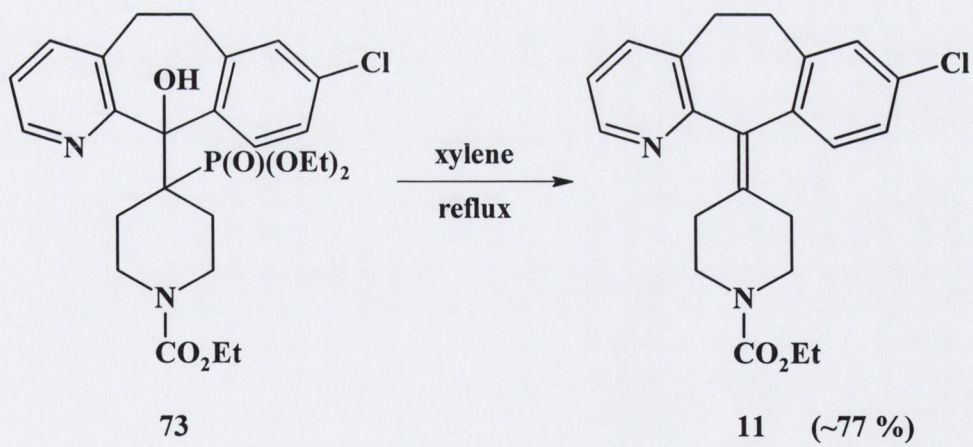
Scheme 1.19: Synthesis of Loratadine **11** from the cycloheptapyridine **69**.

A similar process to obtain the carbamate **11** was reported by Doran and O'Neill.[40] In this case the preparation of Loratadine **11** was accomplished by a Horner-Emmons reaction and subsequent pyrolysis of the product. Diethyl *N*-ethoxy-carbonylpiperidine-4-phosphonate **72** was deprotonated by, *e.g.* lithium diisopropylamide (LDA) and to this was added the tricyclic ketone **42**. This process yielded an oxy-anion intermediate, which was protonated with acetic acid to yield the alcohol **73** (**Scheme 1.20**).



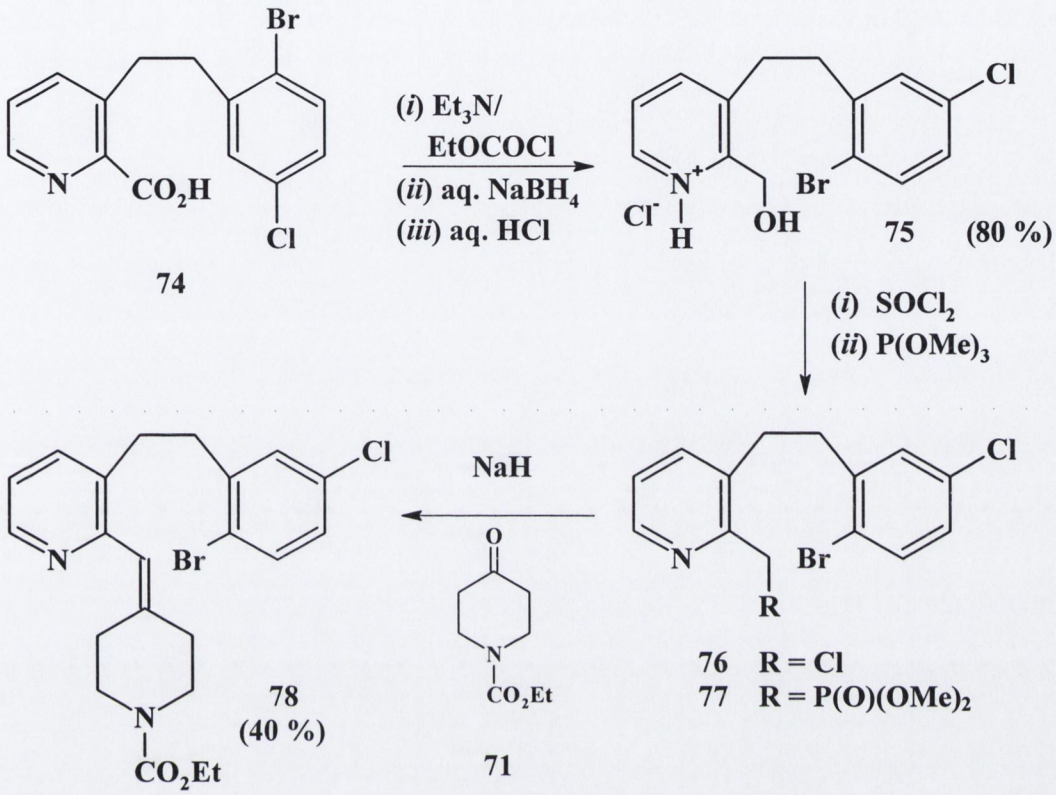
Scheme 1.20: Preparation of the alcohol **73** *via* Horner-Emmons reaction.

Pyrolysis of the β-hydroxyphosphonate **73** in refluxing xylene gave ~77 % of **11** (**Scheme 1.21**).



Scheme 1.21: Pyrolysis of the alcohol **73** to give Loratadine **11**.

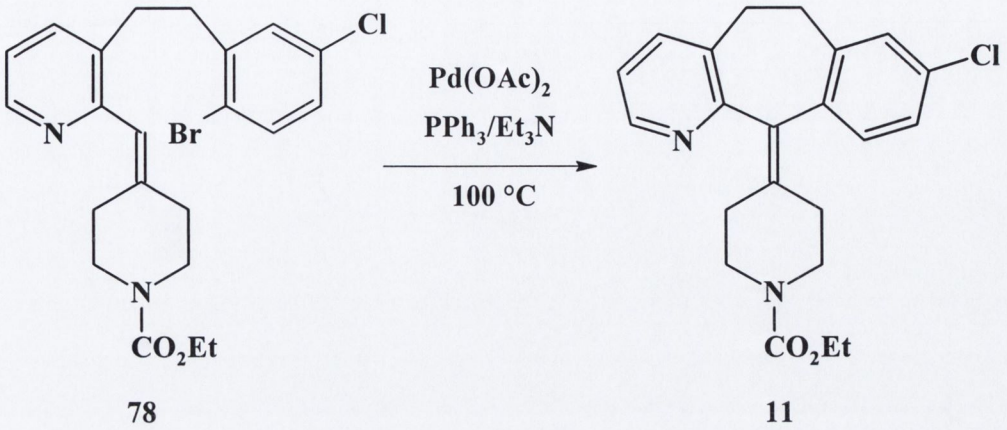
In the processes shown above (**Scheme 1.19** and **1.20/1.21, p24, 25**) the tricyclic structure is formed prior to the attachment of the piperidyl ring. The synthetic route described in two further Spanish patents[41] discloses a rather different approach towards the ethyl carbamate **11**.



Scheme 1.22: Alternative preparation of Loratadine **11** *via* a Heck reaction.

Using Schumacher's route[35] the acid **74** was prepared in a multi-step synthesis (*cf.* **Scheme 1.16** and **1.17, p22, 23**) that included lithiation, alkylation and hydrolysis of amide intermediates. The hydrochloride-salt of the alcohol **75** was obtained in 80 % yield when the acid **74** was firstly reacted with ethyl chloroformate and triethylamine, then with aqueous sodium borohydride, and finally acidified with hydrochloric acid (**Scheme 1.22**). Treatment of the alcohol **75** with thionyl chloride afforded compound **76**, which was then refluxed with trimethyl phosphite to give the Horner-Emmons reagent **77**. The latter was dissolved in THF, deprotonated with sodium hydride and reacted with *N*-(ethoxycarbonyl)-4-piperidone **71** which yielded 40 % of the unsaturated ethyl carbamate **78**.

In the final step of this synthetic route (**Scheme 1.23**) the intermediate **78** was cyclised at 100 °C in DMF under Heck conditions to give Loratadine **11**.

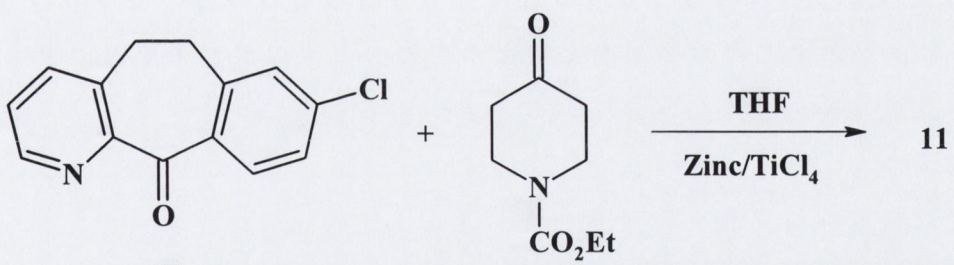


78 **11**

Scheme 1.23: Cyclisation of the piperidyl derivative **78** under Heck conditions.

Alternatively, the cyclisation step shown in **Scheme 1.23** can be carried out in a slightly modified reaction described in a Canadian patent[42] where a combination of $Pd(OAc)_2$, K_2CO_3 and Bu_4NCl was used to yield the desired antihistamine **11**.

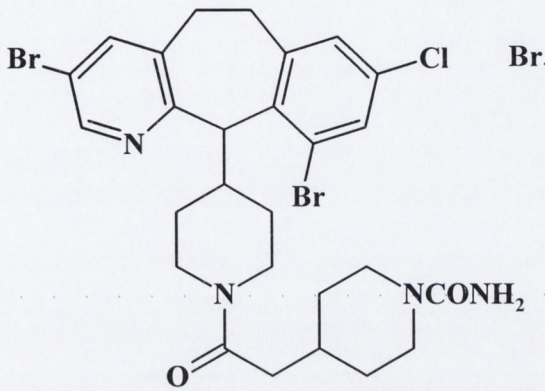
Loratadine **11** was also prepared[43] by means of a McMurry reaction.[53] The tricylic ketone **42** was reacted with *N*-(ethoxycarbonyl)-4-piperidone **71** (**Scheme 1.24**) in the presence of a low-valent titanium species to give the target compound **11**.



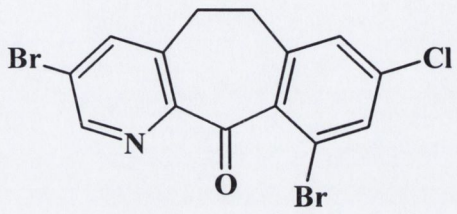
42 **71**

Scheme 1.24: Preparation of Loratadine **11** by means of a mixed McMurry reaction.

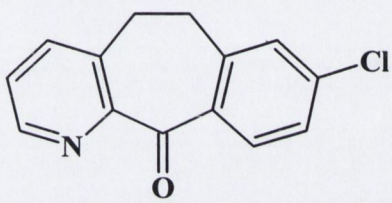
Recently, Poirier and co-workers[44] presented a modification of the synthetic route by Schumacher *et al.*[35] In their effort to synthesise the Loratadine derivative **79**, Grignard- and organolithium-induced anion acylations were investigated. Those reactions proved to be stereo- and chemoselective and gave good to excellent yields. Beside the tricyclic ketone **80**, which was needed for the preparation of **79**, the 8-chloroderivative **42** was also prepared using this method.



79

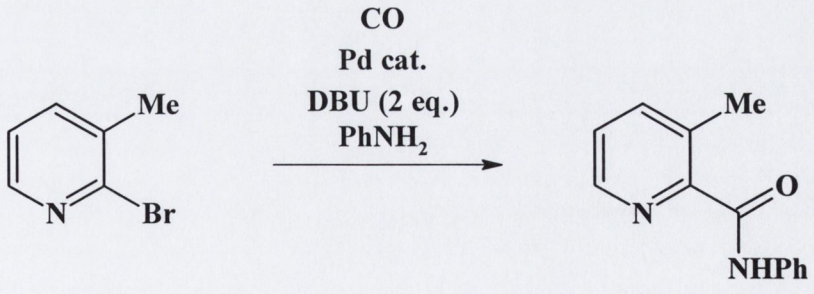


80



42

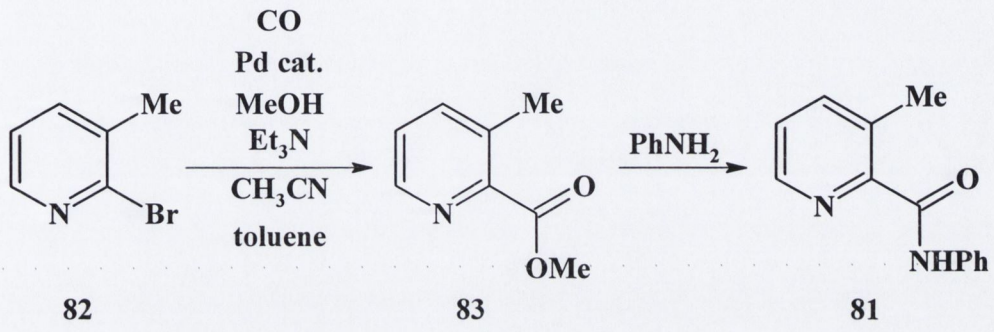
The synthesis of the tricycle **42** started with the preparation of the pyridyl amide **81**, which was obtained *via* two methods. For example, a Pd-mediated amino-carbonylation between 2-bromo-3-methylpyridine **82** and aniline (**Scheme 1.25**) gave the desired compound **81** in moderate yields (59 %). This process is rather expensive as, besides the need for a palladium catalyst, a two-molar excess of the preferred[44] base 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) is required.



82 **81 (59 %)**

Scheme 1.25: Palladium-mediated aminocarbonylation of the bromopyridine **82**.

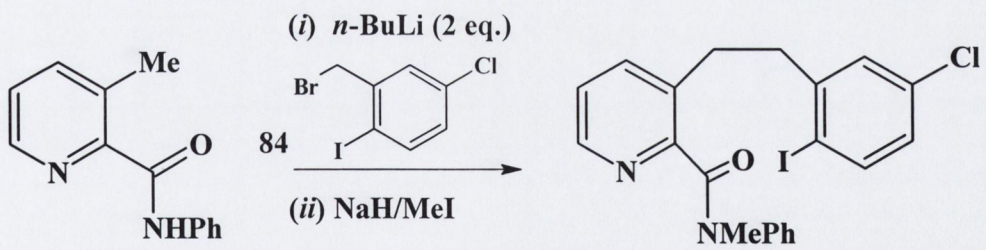
The second approach towards the secondary amide **81** is similar to the one described in the previous Scheme. Again, the 2-bromopyridine derivative **82** was reacted with carbon monoxide in an autoclave in the presence of a Pd-catalyst and base. This time however, the amine was replaced by methanol to yield methyl 3-methylpicolinate **83** which was subsequently converted into the pyridyl amide **81**. This two-step synthesis is depicted in **Scheme 1.26**, however, no detailed reaction parameters have been provided[44] for this process.



82 **83** **81**

Scheme 1.26: Alternative two-step amide synthesis from 3-methyl-2-bromopyridine **82**.

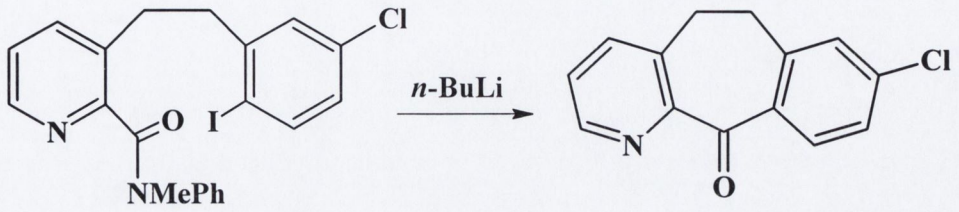
In the next step, compound **81** was lithiated and alkylated with the benzylic bromide **84** to yield an extended amide, which was subsequently converted into the tertiary amide **85** by means of methyl iodide and sodium hydride. The synthesis of the substituted benzylbromide **84** was reported[44] to proceed in excellent overall yield. However, the two alkylation steps shown in **Scheme 1.27** were less successful and a total yield of 64 % was obtained.



81 **85** **(64 %)**

Scheme 1.27: Lithiation of the amide **81** and sequential alkylations with the substituted benzyl bromide **84** and methyl iodide.

The cyclisation of **85** was accomplished by means of an intramolecular acylation reaction carried out by transmetallation of the aryl iodide using either *n*-butyl-lithium or various Grignard reagents. In case of the 8-chloro tricyclic ketone **42**, prepared as shown in **Scheme 1.28**, the best results were achieved with *n*-BuLi, and the reported yield was 91 %.

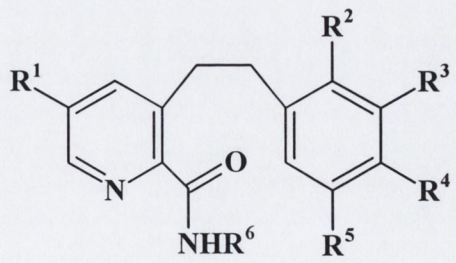


85 **42** **(91 %)**

Scheme 1.28: *n*-Butyllithium-induced cyclisation of the tertiary amide **85**.

Incorporating the procedure published by Schumacher *et al.*[35] makes this overall route even more expensive as now at least three equivalents of *n*-butyllithium per mole of product **42** are required for the entire synthesis. Additionally, the carbonylations were conducted under a pressure of about 80 psi and involved the use of toxic carbon monoxide, which also contributes to the disadvantages of this route.

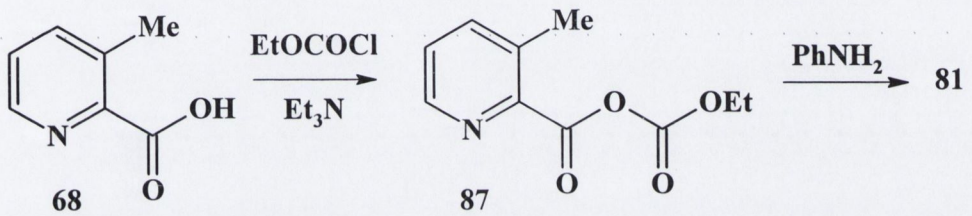
One of the most recent preparations of the tricyclic ketone **42** and similar compounds was reported in the patent literature at the end of 2002. There, Bernard *et al.*[45] described a synthetic route involving the preparation and cyclisation of amides of type **86**. This new approach towards the Loratadine precursor **42** requires one step less than the route previously reported by Schumacher *et al.*[35b]



86 R^{1-5} **= H, Br, Cl, F, alkyl or alkoxy** R^6 **= aryl, heteroaryl**

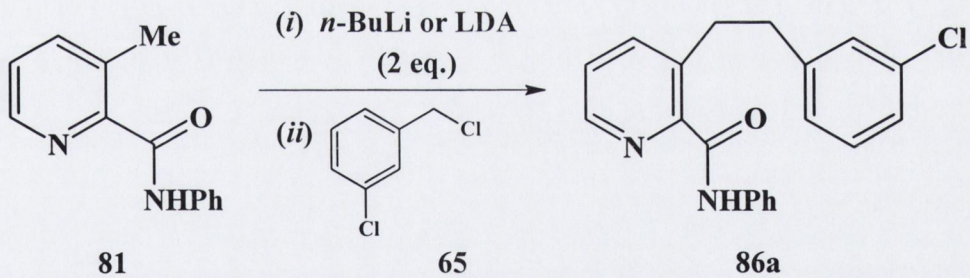
The procedure that is outlined below shows the preparations of the amide intermediate **86a** ($R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Cl$, $R^6 = Ph$) and of the tricyclic ketone **42**, and may serve as an example for a large number of experiments that were conducted.[45]

The preparation of the pyridyl amide **81** was achieved by the aminocarbonylation described in **Scheme 1.25 (p28)**. Yet another strategy[45] towards **81** involved the reaction between 3-methylpicolinic acid **68** and a chloroformate in the presence of an organic base at low temperatures (–30 to 0 °C). This process afforded the mixed anhydride **87** which was subsequently converted into the derivative **81** by the addition of aniline (**Scheme 1.29**). No yields have been reported[45] for this reaction.



Scheme 1.29: Amide synthesis *via* the mixed anhydride **87**.

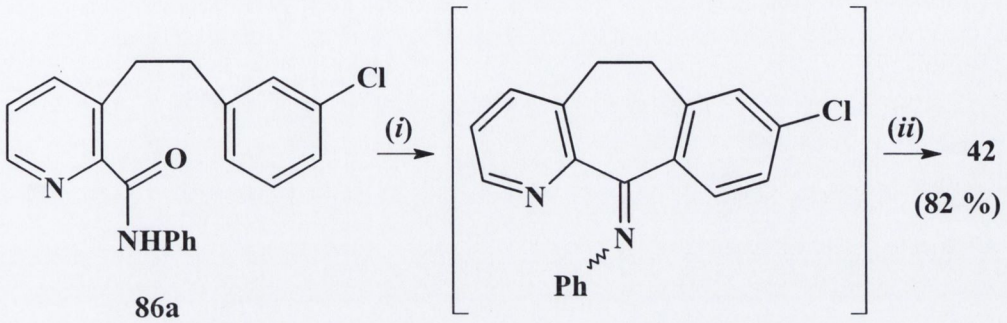
The anion of the amide **81** was then alkylated with 3-chlorobenzyl chloride **65** to give the diarylethane **86a**.



Scheme 1.30: Alkylation of the dianion of the amide **81**.

The extended amide **86a** was obtained in excellent yields (**Scheme 1.30**). However, like in the Schumacher[35] method the deprotonation of the methylpyridine **81** required at least two mole-equivalents of a strong base, preferably *n*-butyllithium or LDA.

A variety of dehydrating reagents, Lewis acids, superacids and solvents was used[45] in the cyclisation reaction shown in **Scheme 1.31**. Typical combinations were P_2O_5-CF_3SO_3H in chlorobenzene, P_2O_5 in dichloroethane, $POCl_3$-CF_3SO_3H in chlorobenzene, PCl_5-$AlCl_3$ in dichloromethane and PCl_5-$AlCl_3$ in chlorobenzene.

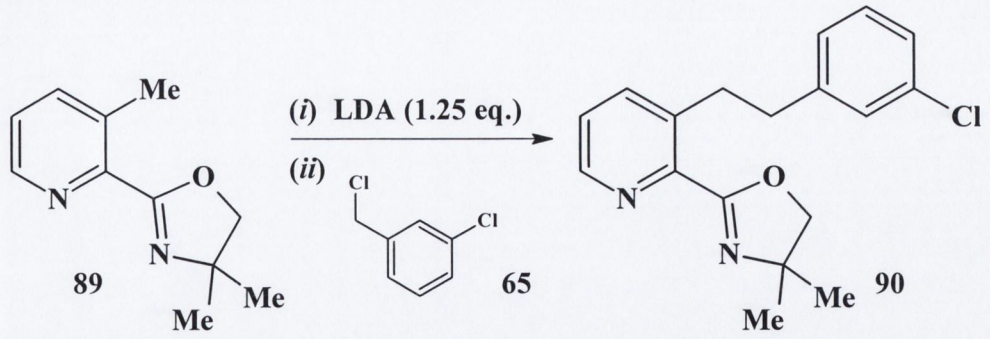


86a **88**

Scheme 1.31: Cyclisation of the amide **86a** *via* the imine intermediate **88**. Reaction conditions: (*i*) dehydrating reagent, *e.g.* PCl_5; Lewis acid, *e.g.* $AlCl_3$, or super acid, *e.g.* CF_3SO_3H; solvent, *e.g.* dichloroethane or chlorobenzene (*ii*) H_2O, hydrolysis.

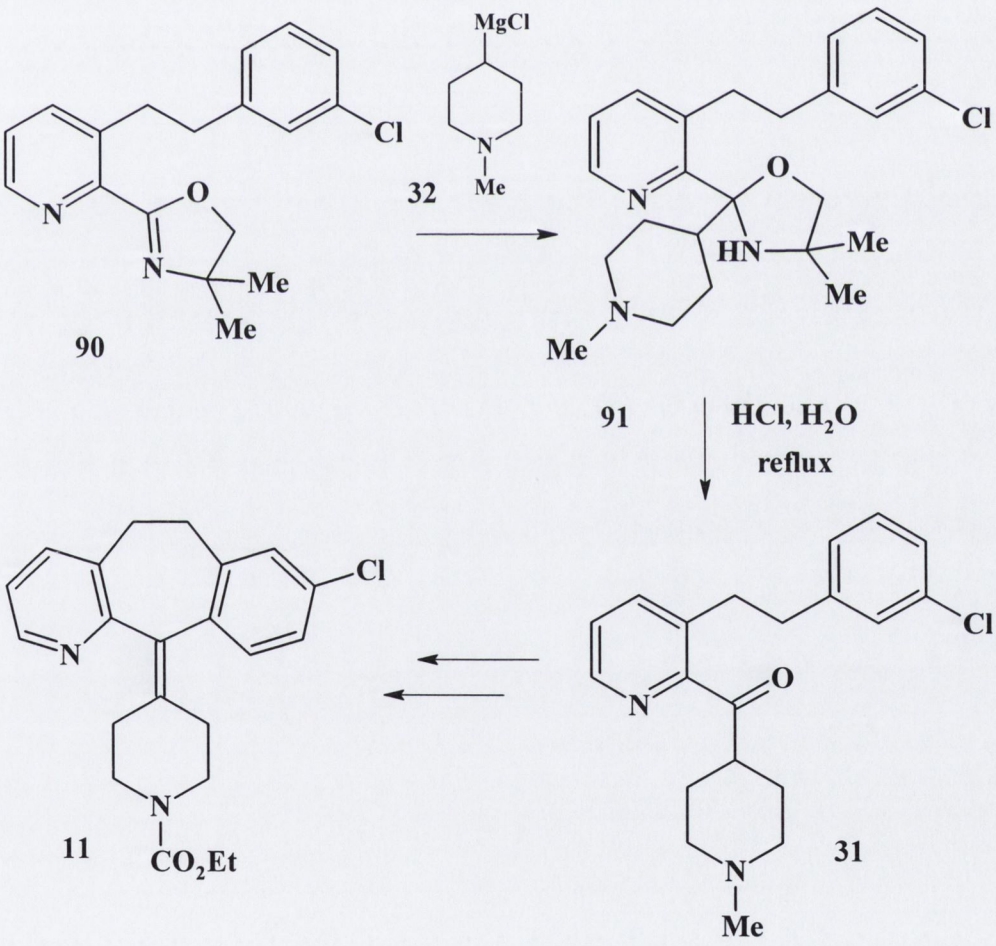
The best yield reported for the cyclisation was 82 %, which is similar to the yield achieved by Villani *et al.*[18] in the Friedel-Crafts acylation of the acid chloride **44** using $AlCl_3$ in benzene. The major advantage and inventive step of this new method is the reduction of number of steps needed for the preparation of the ketone **42**. In a previous procedure[35b] the tertiary butyl amide **63** had to be deprotected after the lithiation/alkylation step and the resulting carboxylic acid **45** or the nitrile **26** had to be isolated and purified prior to cyclisation. The amide **86a**, however, can be cyclised directly to give the imine intermediate **88** which is hydrolysed to the 8-chloro derivative **42** in a one-pot process.

Only recently, Cannata and Cotarca[46] reported on the synthesis of Loratadine **11** *via* the novel oxazoline **89**, which was prepared from 2-cyano-3-methylpyridine **62** using a procedure described by Fryzuk and co-workers.[54] Alkylation of the anion of the cyclic amide **89** (**Scheme 1.32**) with the benzylic chloride **64** required only 1.25 equivalents of expensive LDA, which is a significant improvement to the use of at least two moles of *n*-butyllithium in the Schumacher[35] route.



Scheme 1.32: Alkylation of the anion of the oxazoline **89**.

The extended oxazoline **89** can be employed in a Grignard reaction to give the piperidyl derivative **90**. Subsequent hydrolysis of the latter compound (**Scheme 1.33**) yields the ketone **31**, which can be cyclised according to the methods[16,35] described above to yield Loratadine **11**.



Scheme 1.33: Grignard reaction and hydrolysis of the oxazoline **91** to give the ketone intermediate **31**.

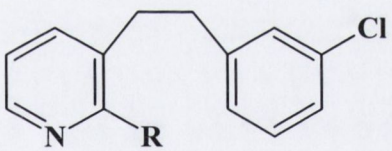
The cyclic amide **89** was also hydrolysed to the corresponding carboxylic acid **45**, which was then treated with thionyl chloride. The resulting acid chloride **44** was reacted under Friedel-Crafts conditions, similarly to the method described by Villani,[18] which afforded the tricyclic ketone **42** in 62 % of the theoretical yield. Beside the reduction of expensive base needed in the process of making Loratadine **11**, the strategies presented by Cannata and Cotarca[46] include fewer reaction steps and involve less toxic and less dangerous reagents than previous methods. However, the preparation of the oxazoline **89** still requires the use of very expensive 2-cyano-3-methylpyridine **63**.

1.6 Retrosynthesis

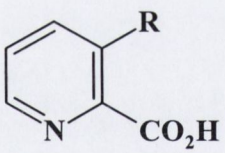
Basically, two broad approaches towards Loratadine **11** have been employed in the synthetic routes presented so far. In the first approach the protected piperidine group is attached to a dihydrostilbazole prior to ring-closure. In the second approach, a tricyclic ketone is formed first, and this is then reacted with the Grignard reagent **32** derived from *N*-methyl-4-chloropiperidine.

In both approaches either the nitrile **26** or the acid **45**, play an important role. As described above, the introduction of a cyano group to the *ortho*-position of the pyridine ring is rather complicated and requires the use of very toxic reagents. Therefore, the main target of this project was to find a way that gives easy access to the nitrile **26** or to one of its derivatives, preferably the corresponding carboxylic acid **45**, by employing less expensive and less toxic reagents.

The first question that arose was how to link the aromatic with the heteroaromatic ring structure. In the synthetic routes presented in **Section 1.5 (p9)**, the *meta*-position of the pyridine ring was initially substituted by either a methyl, carboxyester or formyl group.



26 **R = CN**
45 **R = CO_2H**

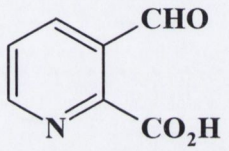


68 **R = Me**
92 **R = CO_2Alk**
93 **R = CHO**

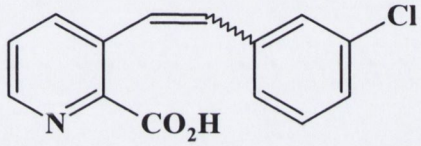
Lithiation of the methyl group of **68** is a very costly process, because usually two moles of lithium reagent are required. Furthermore, double alkylation at the methyl group occurs as an unwanted side-reaction. Additionally, the carboxyl group must generally be protected prior to lithiation, which involves further preparative steps, including the isolation and purification of the protected compound.

The condensation of pyridine carboxyesters with 3-chlorobenzyl cyanide **18** is not a very good starting point because it leads to a keto-nitrile which then has to be converted into the acid **45** in two additional steps, *i.e.* hydrolysis of the nitrile group with subsequent decarboxylation, and then reduction of the ketone to a methylene group by means of a Wolff-Kishner reaction (*cf.* **Section 1.5.1, p10**).

However, a compound like **93**, bearing an aldehyde function in the 3-position and a 2-carboxyl group (which might have to be protected), could possibly be reacted with a dialkyl 3-chlorobenzylphosphonate in an inexpensive Horner-Emmons reaction, as was described for pyridine-3-carboxaldehyde in **Section 1.5.4 (p18)**. Alternatively, a Wittig reaction could be conducted to couple the benzene ring with the pyridine ring to yield the stilbazole **94**.

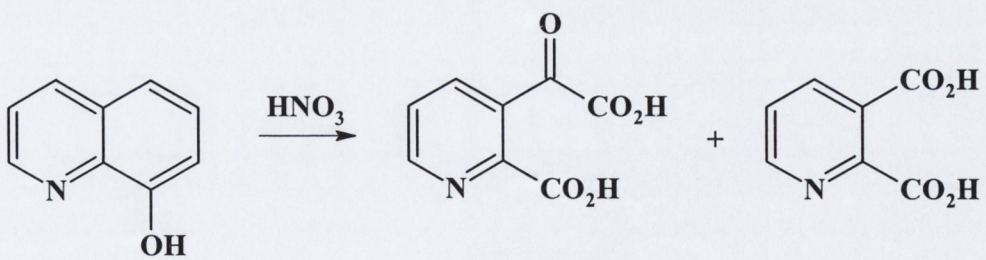


93



94

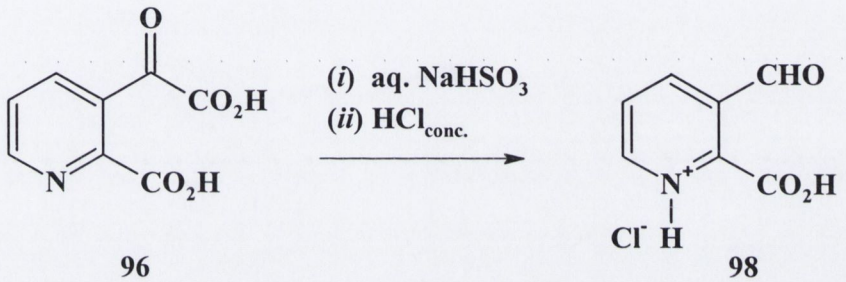
3-Formylpicolinic acid **93** has been described by Bottari and Carboni[55] and also by Makki *et al.*[56] The first-named authors obtained the acid **93** in a two-step reaction in which 8-hydroxyquinoline **95** was oxidised by means of nitric acid at 0-5 °C to yield 2-carboxy-3-pyridineglyoxylic acid **96** together with quinolinic acid **97** (**Scheme 1.34**).



95 **96 (24 %)** **97**

Scheme 1.34: Oxidation of 8-hydroxyquinoline **95** to give the keto-acid **96** and quinolinic acid **97**.

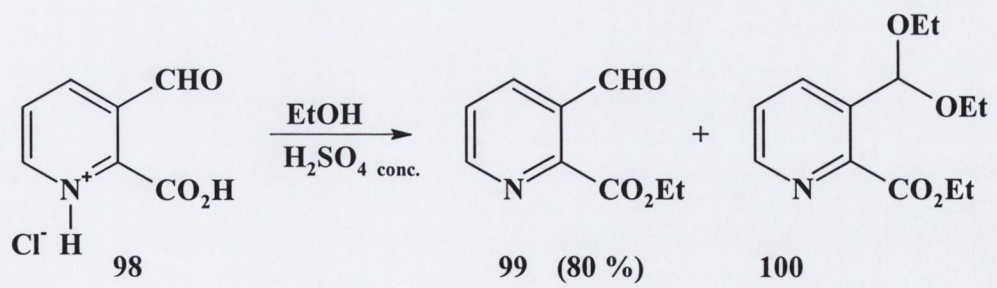
The keto-acid **96** was obtained in only 24 % yield in this reaction, the principal product being quinolinic acid **97**. The keto-acid **96** was converted into the aldehydo-acid **93** by treatment with alkaline sodium *meta*-bisulfite followed by a tedious work-up. The preparation of the keto-acid **96** *via* oxidation of 8-hydroxyquinoline **95** with nitric acid according to Bottari and Carboni[55] was later adapted by Makki *et al.*[56] and similar results were obtained. However, when the conversion of the keto-acid **96** into the aldehyde **93** according to Bottari's method was attempted, only an unidentified product was isolated. Instead, Makki *et al.* sequentially treated the keto-acid **96** with aqueous sodium *meta*-bisulfite and concentrated hydrochloric acid to afford the hydrochloride-salt of 3-formylpicolinic acid **93** (**Scheme 1.35**). No yields were given for this reaction.



96 **98**

Scheme 1.35: Preparation of the hydrochloride-salt **98** of 3-formylpicolinic acid **93**.

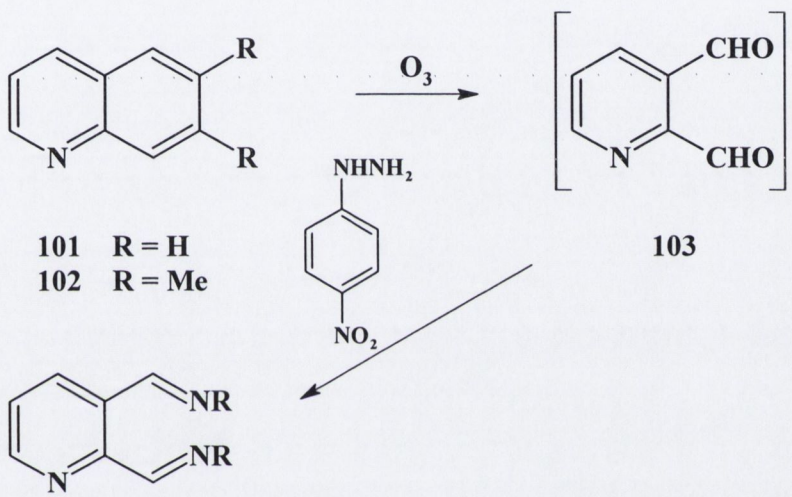
In a further reaction[56] the pyridinium-salt **98** was treated with concentrated sulfuric acid and ethanol to obtain the ethyl ester **99** in 80 % of the theoretical yield with the acetal **100** as a by-product (**Scheme 1.36**). The ester **99** was then utilised in cyclisation reactions with ethanolamines to produce 2-aryl-2,3-dihydrooxazolo-[3,2:1,2]pyrrolo[3,4:3,2]-pyridin-5-ones.



98 **99** **(80 %)** **100**

Scheme 1.36: Esterification of the acid **98** to give the ethyl ester **99** and the acetal **100**.

Alternatively, the oxidation of 8-hydroxyquinoline **95** can be carried out by means of potassium permanganate, hydrogen peroxide in the presence of copper sulfate and sulfuric acid, ozone or by electrolytic oxidation.[57] However, these methods have been predominantly used to produce quinolinic acid **97** and, apart from the reactions described by Carboni *et al.*[55] and by Makki *et al.*,[56] only one preparation of pyridinealdehydes *via* the oxidation of quinolines has been reported.[58] Here, where Wibaut and Boer reacted quinoline **101** and 6,7-dimethylquinoline **102** with ozone, not the pure pyridine dialdehyde **103** but only its derivatives, *e.g.* the dihydrazone **104**, could be isolated (**Scheme 1.37**). A more detailed description of the history of ozonolyses of quinolines, including the experiments conducted by Wibaut and Boer, will be given in **Chapter 2**.



101 R = H
102 R = Me

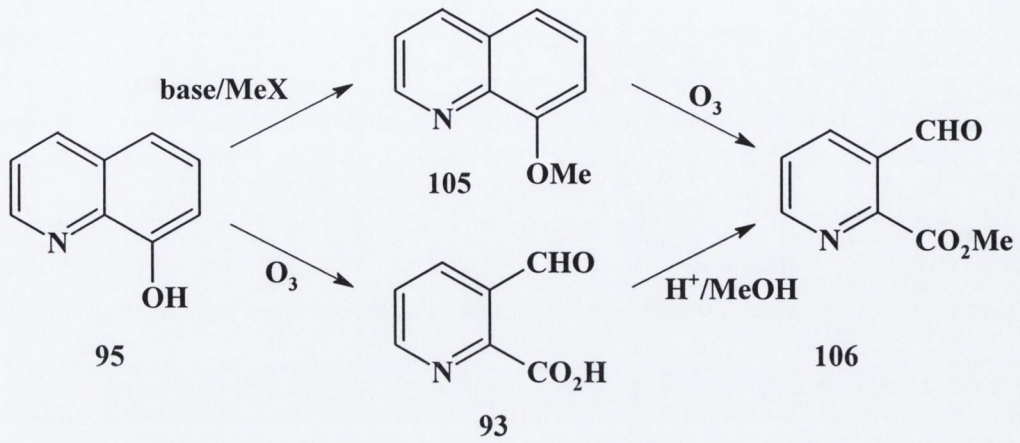
103

104 R = NH-*p*-$C_6H_4NO_2$

Scheme 1.37: Ozonolysis of quinoline **101** and of 6,7-dimethylquinoline **102**.

Although these results were not very encouraging, the preparation of the aldehyde **93** *via* the ozonolysis of a suitable quinoline, *e.g.* 8-hydroxyquinoline **95** still appeared to be a promising method. With regard to the later Horner-Emmons or Wittig reactions that would be needed to form a stilbazole, it would be necessary to protect the carboxylic acid group of **93**. It was considered that this might be achieved in two ways. Either 8-hydroxyquinoline **95** could be alkylated to yield an ether, for example 8-methoxyquinoline **105**, which would then be ozonised to give the methyl ester **106**, or the latter would be prepared after the ozonolysis of **95** by esterification of the carboxyl group of **93** with a suitable alcohol (**Scheme 1.38**).

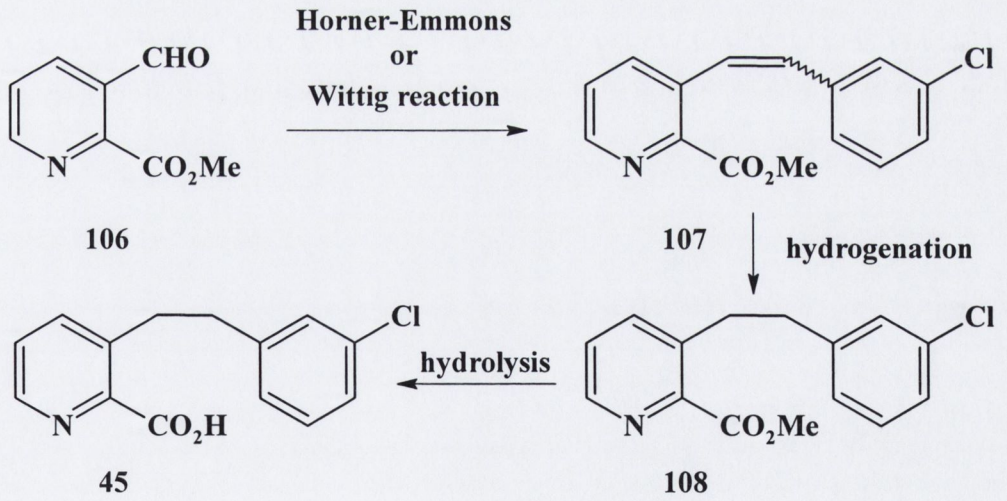
In the present case it was decided to choose the first option, *i.e.* to methylate 8-hydroxyquinoline **95** prior to ozonolysis.



MeX = methylating agent, *e.g.* MeI or $(MeO)_2SO_2$

Scheme 1.38: Two possible preparations of the carboxylic acid ester **106**.

The next step of this route would then be a Horner-Emmons or Wittig reaction of the aldehydo ester **106** to give the stilbazole **107**. Finally, the desired acid **45** would be obtained by hydrogenation of **107** and subsequent hydrolysis of the resulting ester **108** (**Scheme 1.39**).



Scheme 1.39: Synthetic strategy towards the 3-phenethylpicolinic acid **45**.

1.7 Objectives/Strategy I

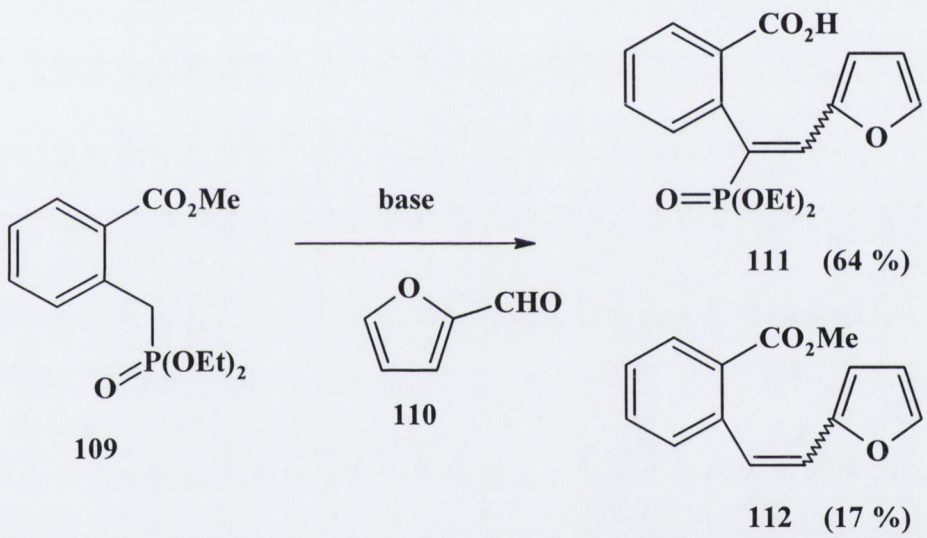
In summary, the pivotal acid **45**, required for the synthesis of Loratadine **11**, might be obtained by the following strategy:

- *O*-Alkylation of 8-hydroxyquinoline **95**
- Ozonolysis of an 8-alkoxyquinoline, such as 8-methoxyquinoline **105**
- Horner-Emmons or Wittig reaction of the aldehydo ester **106**
- Hydrogenation of the stilbazole **107**
- Saponification of the ester **108**

Preparing compound **45** according to this route was the first project of this Thesis. The five reactions outlined above will be discussed in detail in **Chapter 2**.

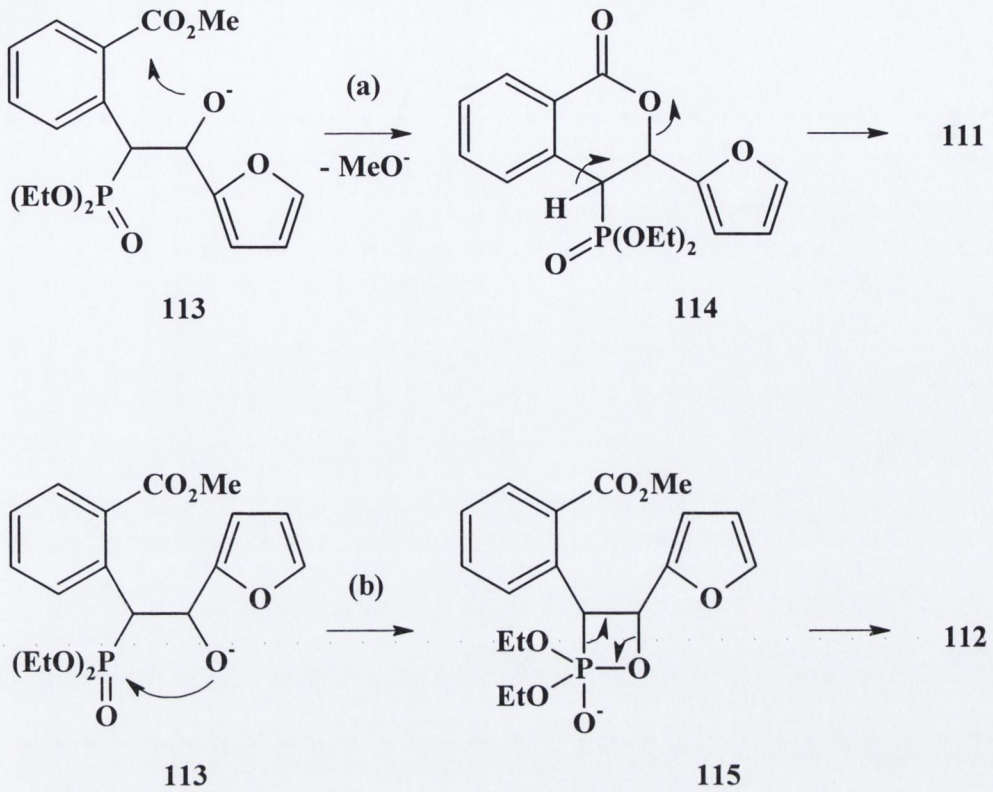
1.8 Stobbe-like[59] condensations

The strategy to obtain the pyridine-2-carboxylic acid derivative **45**, outlined in **Scheme 1.39 (p39)**, includes the synthesis of the stilbazole **107**, which was considered accessible *via* two methods: a reaction between the aldehyde **106** and an anion derived from a benzylphosphonate or with an ylid prepared from a benzyltriphenylphosphonium salt. For the reasons of cost-efficiency and facile work-up procedures, a Horner-Emmons reaction would be preferred. However, a recently discovered[60] side-reaction between the anion of the benzylphosphonate **109** and 2-furaldehyde **110** casted some doubt on the feasibility of this concept. As shown in **Scheme 1.40**, the reaction between the deprotonated phosphonate **109** and the aldehyde **110** produced mostly the novel vinylphosphonate **111** (64 %), while the expected carboxy ester **112** was only obtained as the minor product (17 %).



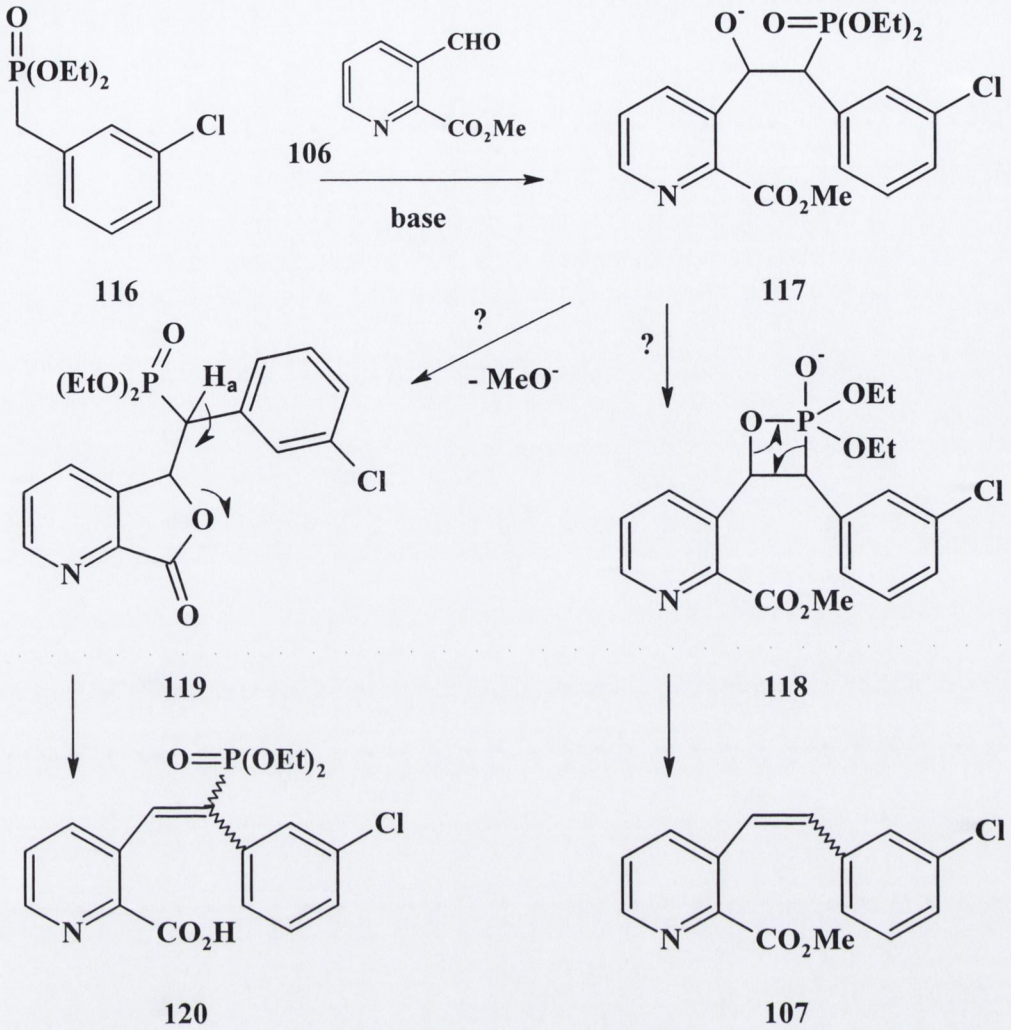
Scheme 1.40: Unexpected outcome of a Horner-Emmons reaction.

The formation of the vinylphosphonate **111** (**Scheme 1.41**) can be rationalised in the following way: nucleophilic attack of the anion of **109** at the carbonyl group of the aldehyde **110** yields the oxy-anion **113**, which undergoes cyclisation (**a**) to give the lactone **114**. A Stobbe-like[59] β-elimination of carboxylate ion then yields the deprotonated form of the unsaturated phosphonic acid ester **111**. The mechanism (**b**) *via* the oxaphosphetane **115** leads to the "normal" Horner-Emmons product **112**.



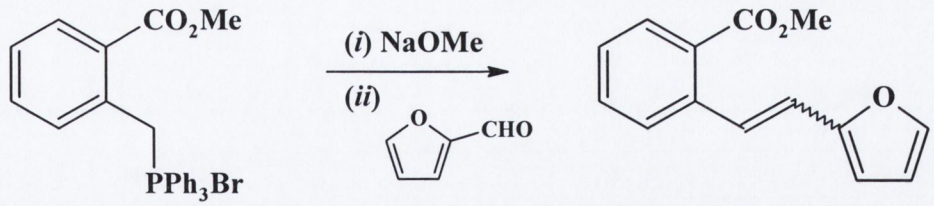
Scheme 1.41: Two possible mechanistic pathways from the oxy-anion **113**.

The occurrence of this unprecedented by-product **111** indicates possible difficulties in the preparation of the stilbazole **107** *via* Horner-Emmons reactions. Although in the present case the formyl and the carboxyl ester group are on the same molecule, a similar side-reaction might be expected (**Scheme 1.42**). Instead of following the mechanistic pathway of the Horner-Emmons olefination, *i.e.* the addition of 3-formyl-2-carbomethoxypyridine **106** to deprotonated diethyl 3-chloro-benzylphosphonate **116** to give the oxy-anion **117**, which cyclises to the oxaphosphetane **118** and finally yields the stilbazole **107**, the reaction might also proceed *via* a Stobbe-like mechanism. The five-membered lactone **119** could be formed by cyclisation of the oxy-anion **117** and subsequent abstraction of proton H_a and elimination of carboxylate ion would then lead to the formation of the vinylphosphonate **120**.



Scheme 1.42: Possible mechanistic pathways to yield either the vinylphosphonate **120** or the stilbazole **107**.

Recognising that the Horner-Emmons reaction shown in **Scheme 1.40** yielded mostly an unwanted by-product, O'Neill[60] decided to prepare the desired unsaturated ester **112** *via* a conventional Wittig reaction between the deprotonated phosphonium salt **121** and 2-furaldehyde **110**. This reaction, depicted in **Scheme 1.43**, was successful and produced the expected stilbene **112** as a mixture of (*E*)- and (*Z*)-isomers in good yields, thus showing a possible alternative synthesis of the stilbazole **107** in the present case.



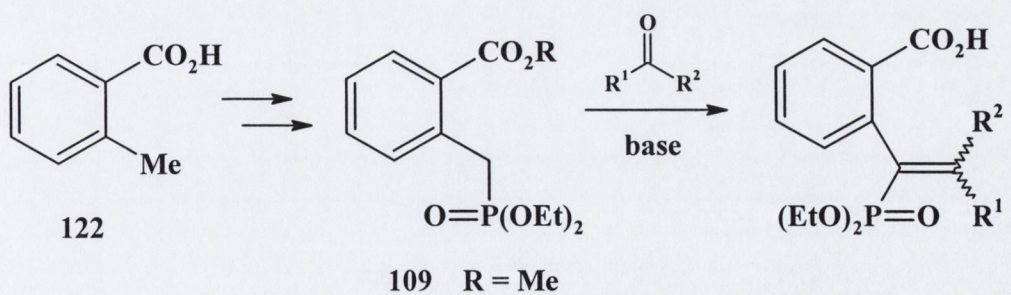
121 **110** **112**

Scheme 1.43: Alternative preparation of the disubstituted alkene **112**.

Independently from the outcome of the different approaches towards the ester **107** required for the synthesis of Loratadine **11**, it was decided to further investigate the reactions between the anions of diethyl 2-(carboalkoxy)benzylphosphonates, *e.g.* the methyl ester **109**, and carbonyl compounds, possibly offering facile access to a variety of novel vinylphosphonates. Initial attempts[60] to synthesise the phenyl analogue of compound **111** had failed and further investigations carried out by Huddleston[61] were only slightly more successful.

1.9 Objectives/Strategy II

The aim of this second project was to explore the scope of the reactions between deprotonated diethyl 2-(carboalkoxy)benzylphosphonates, *e.g.* the methyl ester **109**, easily accessible from *o*-toluic acid **122**, and a number of aldehydes and ketones (**Scheme 1.44**).



122

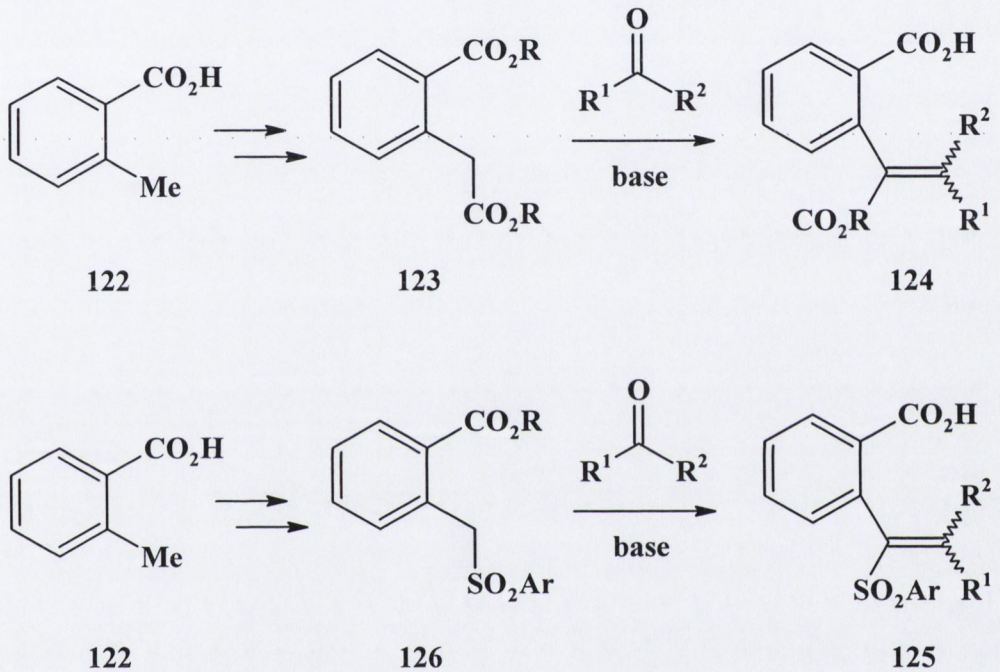
109 R = Me

R = alkyl, R^1 = H or alkyl, R^2 = aryl, heteroaryl or alkyl

Scheme 1.44: Synthetic strategy to obtain vinylphosphonates.

1.10 Novel approach towards vinylsulfones

A literature search revealed[62] that reactions similar to the ones described in **Section 1.8 (p41)** and **Section 1.9 (p44)** have been carried out, using alkyl 2-(carboalkoxy)benzylcarboxylates **123** as substrates (**Scheme 1.45**) yielding the carboxyl ester analogues **124** of the vinylphosphonate **111**. However, so far no reports on the synthesis of sulfonyl-substituted stilbenes **125** *via* Stobbe-like condensations have been published and thus, it was also decided to investigate the reactions between the anion of an alkyl 2-(arylsulfonylmethyl)benzoate **126** and various carbonyl group-containing compounds (**Scheme 1.45**).



R = alkyl, R^1 = H or alkyl, R^2 = (hetero)aryl, Ar = aryl

Scheme 1.45: Stobbe-like[59] condensations of carboxyl- and sulfonyl esters.

1.11 Objectives/Strategy III

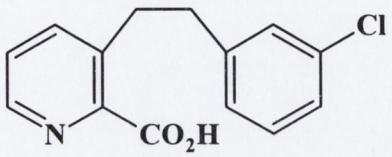
The investigation of Stobbe-like[59] reactions between deprotonated benzyl sulfones bearing esters groups in the *ortho*-position and carbonyl compounds, such as 2-furaldehyde **110**, was the aim of the third project. The results obtained from these reactions are presented in **Chapter 4**.

CHAPTER 2:

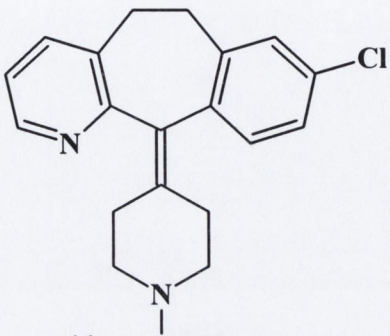
Synthetic approach towards 3-[2'-(*m*-chlorophenyl)ethyl]picolinic acid 45

2.1 Introduction

In this Chapter the synthetic approach towards 3-[2'-(*m*-chlorophenyl)ethyl]-picolinic acid **45**, an important precursor of Loratadine **11**, will be described.

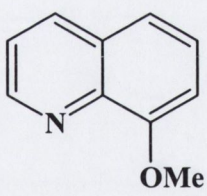


45

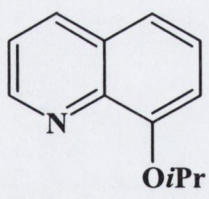


11

The strategy to obtain the picolinic acid derivative **45** is outlined in **Section 1.6** (**Scheme 1.38** and **1.39, p39**) and appears to be rather straightforward as it employs mostly well-known reactions, such as *O*-alkylation, Wittig- and Horner-Emmons olefinations, hydrogenation of stilbazoles and carboxyl ester hydrolysis. The ozonolysis of 8-alkoxyquinolines, such as 8-methoxyquinoline **105** and 8-isopropoxyquinoline **127**, was considered to be the most crucial step in the synthesis towards the acid **45**, hence a short historical overview of this type of reaction will be given now.



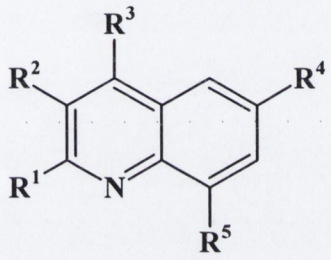
105



127

2.2 Historical overview of ozonolyses of quinoline 101 and quinoline derivatives

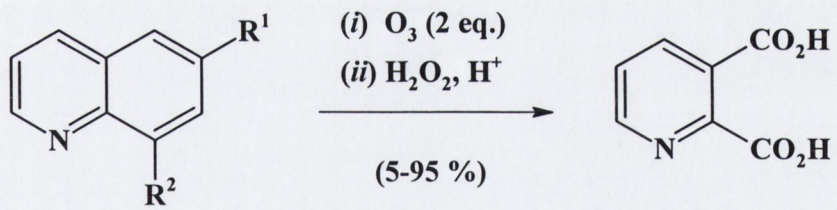
Some of the first ozonolyses of quinolines were performed by Schenck and Bailey,[63,64] who carried out exhaustive ozonolyses of 2,4-dimethyl-8-*s*-butylquinoline **128**, 2,3,4-trimethyl-8-*n*-propylquinoline **129**, 2,4-dimethyl-6-*s*-butylquinoline **130** and 2,3-dimethyl-4-ethyl-8-*n*-propylquinoline **131**. This was done to identify these compounds by analysing their oxidation products, *i.e.*, aliphatic carboxylic acids.



101, 128-131

R^1	R^2	R^3	R^4	R^5	
H	H	H	H	H	101
Me	H	Me	H	*s*-Bu	128
Me	Me	Me	H	*n*-Pr	129
Me	H	Me	*s*-Bu	H	130
Me	Me	Et	H	*n*-Pr	131

In 1949, Lindenstruth and van der Werf[57] investigated the ozonolysis of quinoline **101** and of quinoline derivatives (**95, 132-135**) by reacting each of these compounds with two molar equivalents of ozone in glacial acetic acid (**Scheme 2.1**).



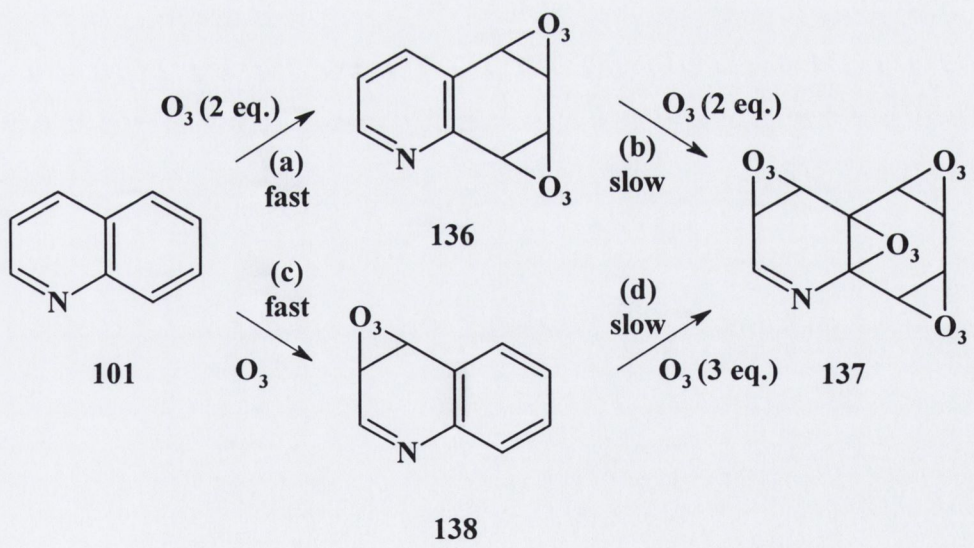
95 $R^1 = H, R^2 = OH$
132 $R^1 = NH_2, R^2 = H$
133 $R^1 = NO_2, R^2 = H$
134 $R^1 = F, R^2 = H$
135 $R^1 = F, R^2 = NH_2$

97

Scheme 2.1: Ozonisation of quinolines followed by an oxidative work-up to yield quinolinic acid **97**.

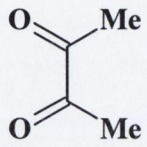
The resulting ozonides were decomposed in an oxidative work-up using hydrogen peroxide to give quinolinic acid **97** in yields ranging from less than 5 % (quinoline **101**) up to 95 % (8-hydroxyquinoline **95**). Further experiments by the same authors[57] showed that the quinolines readily fixed one mole of ozone to the benzene ring, while a second mole was added considerably more slowly. When the benzene ring was mono- or polysubstituted, especially with electron-withdrawing groups, addition of ozone was observed to be slower than with quinoline **101** itself. The ozonides were reported to be very stable and that upon heating they would partially decompose to yield ozone and the former quinoline again.

However, some of these results could not be substantiated by Wibaut and co-workers.[58,65] In kinetic experiments they found that ozone reacted with quinolines at a steady rate firstly on the benzene ring and secondly, more slowly, on the pyridine ring. In their effort to establish a mechanism for the ozonisation of quinolines, Boer, Sixma and Wibaut[65] postulated the formation (a) of a diozonide **136** which upon further addition of ozone (b) yields a tetraozonide **137**. In contrast to Lindenstruth and van der Werf's results it was also found, that to a minor extent (~10 %) the pyridine ring was attacked initially (c) at the 3,4-bond yielding **138** and by further ozonisation (d) the tetraozonide **137** was formed again (**Scheme 2.2**).

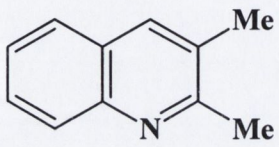


Scheme 2.2: Formation of ozonide intermediates during the ozonolysis of quinoline according to Boer, Sixma and Wibaut.[65]

However, none of the peroxidic products **136-138** could be isolated or characterised and the amount of ozone molar equivalents absorbed does not necessarily imply the formation of the ozonides shown here. The minor reaction *via* pathway (c) was deduced from the considerable amount (10 mol-%) of biacetyl **139** which was detected in the ozonolysis mixture of 2,3-dimethylquinoline **140** (1.5 molar equivalents of ozone).

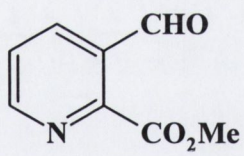


139



140

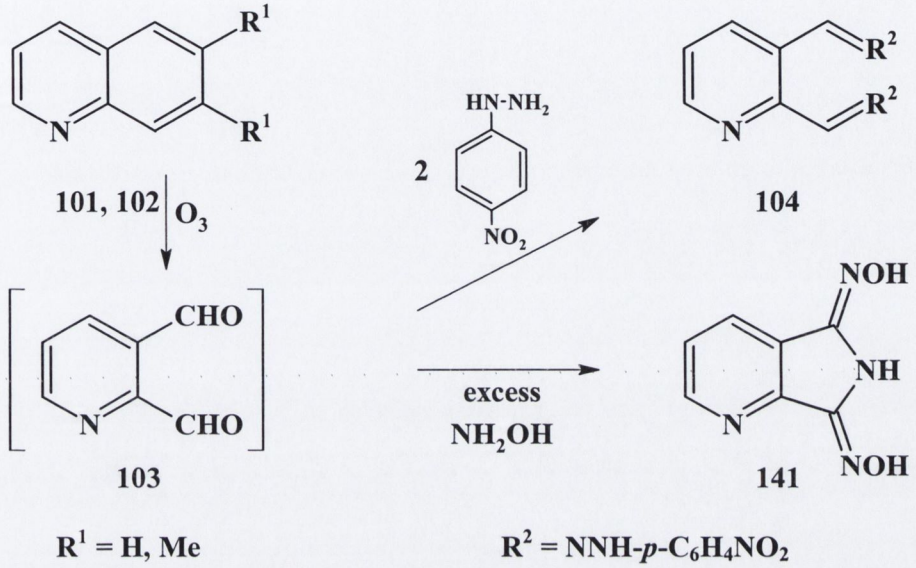
Analogous to pyridine,[66,67] no products were found that indicated the addition of ozone to the 1,2-bond. Also, for the complete ozonolysis of the investigated quinolines only four rather than five molar equivalents of ozone were required. Of special interest for this project was, of course, the ozonolysis of 8-methoxy-quinoline **105**, which after a reductive work-up should theoretically yield 3-formyl-2-carbomethoxypyridine **106**, which might be a suitable precursor in the synthesis of key intermediate **45**.



106

Since the time it was known that the ozonolysis of quinolines gives facile access to 2,3-pyridinedicarboxylic acid **97** and its derivatives, which are important starting materials for the synthesis of herbicides and pressure-sensitive dyes,[68] several investigations[57,68,69] on this reaction have been carried out and the process has been continuously improved. However, as the emphasis in these experiments was put on the synthesis of quinolinic acid **97** and as the latter was obtained after an oxidative work-up, only little is known about the feasibility of producing aldehydic compounds such as **106** *via* the ozonolysis of quinolines.

To the best of the author's knowledge, none of the hypothetical mono- or dialdehydes arising from the ozonolysis of quinolines have ever been isolated so far in their pure form. As has been mentioned in **Chapter 1 (p38)**, Wibaut *et al.*[58] obtained the dialdehyde **103** from the ozonolysis mixtures of quinoline **101** and 6,7-dimethylquinoline **102** only in the form of its derivatives **104** and **141** (**Scheme 2.3**).

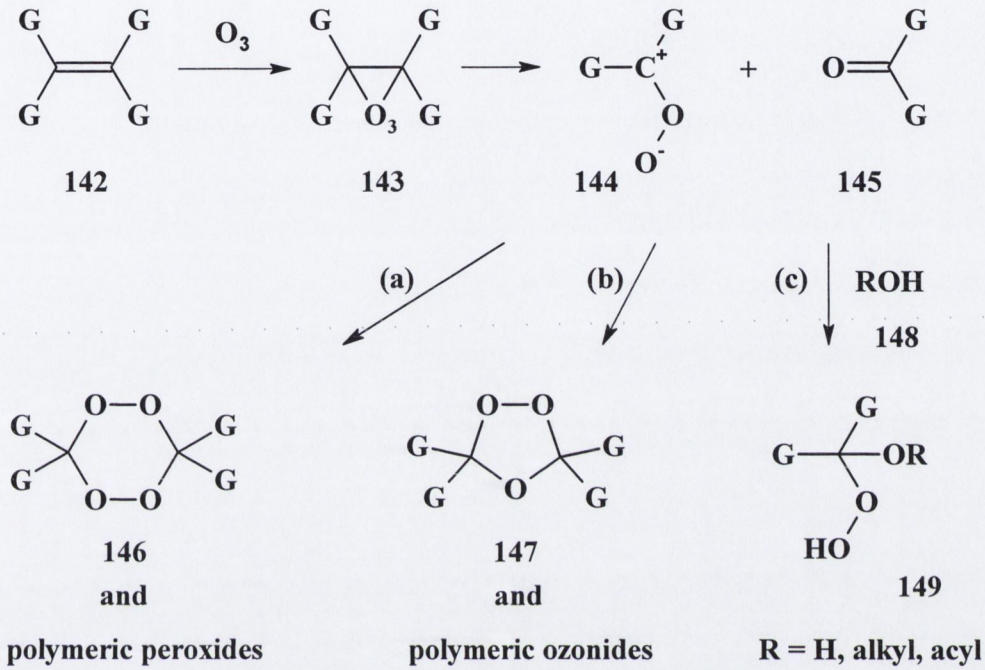


Scheme 2.3: Ozonolyses of quinoline **101** and of 6,7-dimethylquinoline **102**.

The reaction conditions employed by these authors are obviously not very suitable to synthesise the aldehyde **106**, hence a different method had to be found.

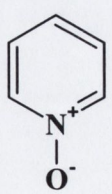
Investigations[70-79] have shown that the outcome of ozonolyses is strongly influenced by three parameters. The first of these parameters is the solvent that is used. It is generally agreed[70] that the ozonisation of an olefin **142** yields initially an unstable molozonide **143** which breaks down quickly to form a zwitterion **144** and a carbonyl compound **145**. The fate of these two entities **144** and **145** is very much dependent on the solvent which is used (**Scheme 2.4**). For example, the ozonolyses conducted by Wibaut *et al.*[58,65] were carried out in aprotic, inert solvents such as chloroform. In this type of solvent mainly the formation of dimeric/polymeric peroxides **146** and (polymeric) ozonides **147** is promoted. Pathway (b) usually predominates in ozonolyses where the carbonyl fragment **145** is an (unhindered) aldehyde, which recombines with the zwitterion **144** to form mono- and polymeric ozonides **147**.

Route (a), in which the zwitterion **144** dimerises/polymerises to give the peroxides **146**, is favoured when the carbonyl compound **145** is a ketone or a hindered aldehyde. Yet another outcome of this reaction is possible when hydroxylic solvents **148**, such as methanol, are employed, in which case the latter might react with the zwitterion **144** according to route (c) to give a hydroperoxide of type **149** as the major product.



Scheme 2.4: Mechanistic pathways for ozonolyses of olefins.

Ozonolyses of olefins dissolved in inert solvents will often follow both pathways (a) and (b) to a certain extent, thus producing a mixture of peroxides and ozonides. However, when a 'participating' solvent like methanol is used, the formation of hydroperoxides will be the major reaction as the concentration of the solvent usually far exceeds that of the other substances present in the mixture.

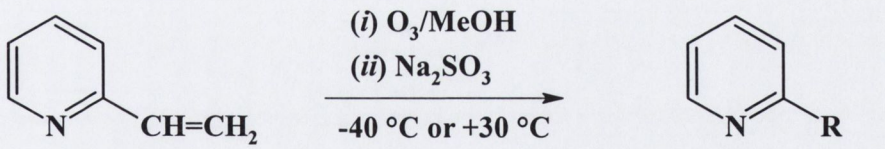


150

The choice of solvent also seems to be responsible for the occurrence or absence of the formation of *N*-oxides when pyridine- or quinoline derivatives are subjected to ozone. It was reported[12] that the addition of *tert*-butanol to an aqueous solution of pyridine prevented the formation of radicals when this mixture was ozonised. Under these conditions the pyridine *N*-oxide **150** was the major product, but when radical development was allowed ammonia, nitrate and amidic compounds were formed.[72] In another two experiments, carried out by Slomp and co-workers,[73] pyridine was believed to have been partially transformed into the *N*-oxide **150** by the action of ozone, however, this compound **150** could never be isolated.

N-Oxidation during the ozonolysis of the alkoxyquinolines **105** and **127** would be a major drawback, as quinoline **101** and its *N*-oxide are known[58,65,74] to react very differently when subjected to ozone. It seems, however, that the formation of pyridine- and quinoline *N*-oxides does not play an important role in ozonisations as there have been no other reports than the ones cited above in which this side-reaction has been observed.

The two remaining important factors in ozonolyses are the temperature and the reducing agent. For example, a high-yielding synthesis of 2-pyridinecarboxaldehyde **151** *via* the oxidation of 2-vinylpyridine **152** with ozone (**Scheme 2.5**) requires very low temperatures during the ozonisation and the reduction process.[75] When this reaction was carried out at –40 °C the desired aldehyde **151** could be isolated in good yields (65 %), however, when the same reaction was conducted at room temperature the principal product was the corresponding carboxylic acid **153**.

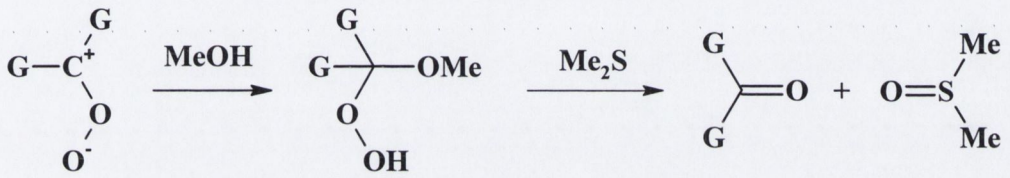


152

151 R = CHO
153 R = CO_2H

Scheme 2.5: Ozonolysis of 2-vinylpyridine **152** in methanol at different temperatures.

Sodium sulfite, sodium iodide, metal-acid combinations[71,76] and trialkyl phosphites[77] are just a few examples of common reducing agents. Unfortunately, some of these reactants exhibit insufficient activity at low temperatures.[78] Further drawbacks observed during the work-up of ozonised solutions include poor selectivity of the reducing agent as well as difficult separation of the oxidised and/or reduced form of the reagent from the desired products.[79] Experiments by Pappas *et al.*[79] have shown that dimethyl sulfide is the most efficient and versatile reagent. It reacts smoothly and selectively with hydroperoxides at low temperatures and, due to a low boiling point, an excess of reagent can easily be evaporated (**Scheme 2.6**). The oxidation product is dimethyl sulfoxide which in most cases can be removed conveniently by aqueous extraction or distillation.[79]



144 **149** **145**

Scheme 2.6: Formation and reduction of the hydroperoxides **149**.

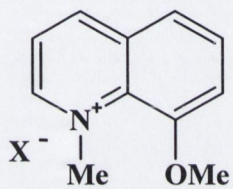
Despite the fact that no mono- or dipyridinecarboxaldehydes have ever been isolated from the oxidation of quinolines with ozone, it was believed that the ozonolysis of 8-methoxyquinoline **105** in methanol, followed by a reductive work-up using dimethyl sulfide, should give access to the desired aldehyde **106**.

2.3 First synthetic approach towards the picolinic acid 45

Two very similar synthetic approaches towards the target compound **45** were attempted, both consisting of five steps. The first synthetic route starts with the methylation of 8-hydroxyquinoline **95**, whereas in the second approach (**Section 2.4, p68**) the hydroxyl group of **95** is protected with an isopropyl group.

2.3.1 Methylation of 8-hydroxyquinoline 95

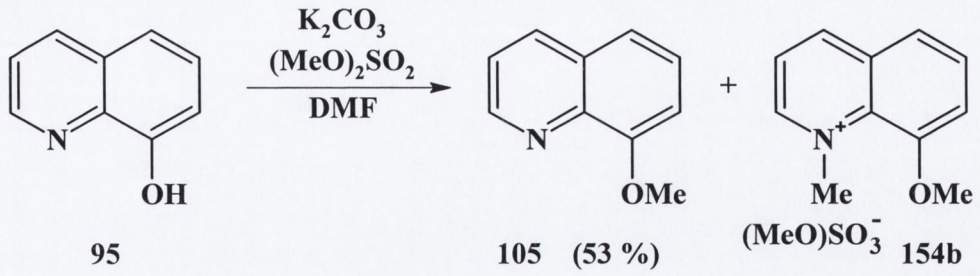
One of the earliest *O*-methylation procedures[80] of 8-hydroxyquinoline **95** dates from the late 19th century and employs methyl iodide as the alkylating agent. However, it was reported[81] that the preparation of 8-methoxyquinoline **105** *via* this method yields substantial amounts of *N*-methylated 8-methoxyquinoline **154a** as a by-product. These claims were supported by the investigations of Khan *et al.*,[82] in which 8-hydroxyquinoline **95** was treated with sodium ethoxide and methyl iodide yielding both products, the ether **105** and the iodide salt **154a** of the dimethylated quinoline. Kaufmann and Rothlin[81] synthesised 8-methoxyquinoline **105** by the action of dimethyl sulfate on 8-hydroxyquinoline **95** in aqueous sodium hydroxide solution. The authors stated that none or only little of the *N*-alkylated quinoline **154b** was formed and that yields were above 70 %.



154a X = I
154b X = $(MeO)SO_3$

Other preparations involved the use of benzenesulfonic acid methyl ester[83] and trimethylsilyldiazomethane[84] as methylating agents. An extended literature search, which included other hydroxyquinolines as starting materials, provided further procedures employing potentially suitable solvent/base systems.[85]

Several moderately successful attempts towards the synthesis of 8-methoxyquinoline **105** were carried out which involved the use of various bases, *e.g.*, sodium hydroxide, sodium hydride or potassium bicarbonate, various alkylating reagents, for example, dimethyl sulfate or *p*-toluenesulfonic acid methyl ester, and various solvents, such as water, acetone or *N*,*N*'-dimethylformamide (DMF). However, none of these reactions yielded the desired methyl ether **105** in more than 53 % yield after purification and the crude product was always accompanied by the dimethylated derivative **154b**. The best result was achieved with a combination of potassium bicarbonate, dimethyl sulfate and DMF (**Scheme 2.7**).



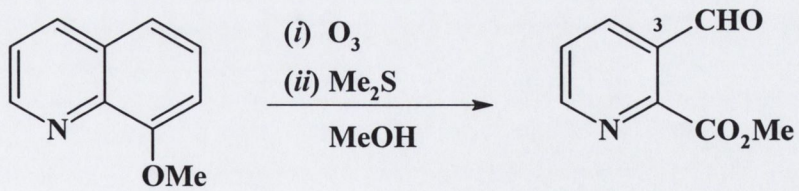
95 105 (53 %) 154b

Scheme 2.7: *O*- and *N*-methylation of 8-hydroxyquinoline **95**.

Separation of the *N*-methylated quinoline **154b** from **105** did not pose any problems and thus an analytical sample of 8-methoxyquinoline **105** was obtained. The ^{1}H nuclear magnetic resonance (NMR) and infrared (IR) spectra of the brown, low-melting crystals (*lit.*[81] m. p. 46-47 °C) showed the expected[86] signals and absorptions, respectively.

2.3.2 Ozonolysis of 8-methoxyquinoline 105

Most of the ozonolyses of 8-methoxyquinoline **105** were carried out in methanol, but in two experiments ethyl acetate was used. Although most of the reactions cited in the text above were carried out at a temperature of or below –40 °C, initially, all preparative steps, the ozonisation as well as the reductive work-up of the intermediates, were carried out at ice-bath temperature. Thus, 8-methoxyquinoline **105** was dissolved in methanol, and was subjected to an ozone/oxygen stream for several hours. A colour change of the solution from dark red/brown to almost colourless indicated the end point of the reaction. The ozonisation of the ether **105** was followed by a reductive work-up using dimethyl sulfide (**Scheme 2.8**).



105 106 (81 %)

Scheme 2.8: Ozonisation of the aromatic ether **105** followed by reductive work-up.

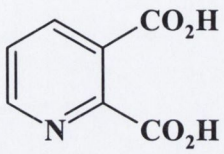
The first ozonolysis yielded a complex mixture of compounds as evidenced by ^{1}H NMR spectral analysis. However, the major product was the desired aldehydo methyl ester **106**. In the proton NMR spectrum a 1H-singlet at δ_H 10.31 ppm is due to the aldehyde proton, and a 1H-doublet of doublets (J_1 5.0 Hz and J_2 1.5 Hz) at δ_H 8.87 ppm corresponds to *H*-6. Another 1H-doublet of doublets at δ_H 8.31 ppm with coupling constants of J_1 7.8 Hz and J_2 1.8 Hz represents *H*-4. The remaining aromatic proton *H*-5 resonates at δ_H 7.81 ppm as a doublet of doublets (J_1 7.8 Hz and J_2 4.8 Hz) and a 3H-singlet at δ_H 3.94 ppm is assigned to the methyl ester protons. The ^{13}C NMR spectrum (**Table 2.1**) of the purified aldehyde **106** provided further evidence for the success of the reaction. Two carbonyl signals appear at δ_C 191.68 (*C*HO) and 165.73 (*C*O_2Me) ppm, respectively. The methyl carbon is represented by the peak at δ_C 52.95 ppm and five more signals appear in the ranges which are predicted[87] for pyridine carbons of compounds such as **106**.

Table 2.1: Chemical shifts δ_C of the aldehydo-ester **106**.

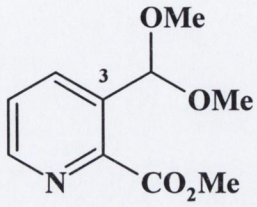
Assignment	Chemical Shift δ_C (ppm)
CH_3	52.95
C-5	126.61
C-3	131.07
C-4	137.56
C-2	149.72
C-6	152.93
CO_2	165.73
*C*HO	191.68

Two strong absorptions in the IR spectrum of the aldehyde **106** at 1710 and 1693 cm^{-1} give evidence for the presence of two C=O bonds of the ester and aldehyde function. Apart from a number of smaller peaks in the upfield region (δ_H 1-4 ppm) of the proton NMR spectrum, most of them probably due to the aliphatic scission products, two major by-products were found.

Each of these two compounds produces a set of three 1H-signals in the aromatic region, similar to the peaks observed for the pyridine protons of the aldehyde **106**. One of these compounds was most likely quinolinic acid **97** which, however, could not satisfactorily be isolated from the reaction mixture. The other compound was separated by column chromatography and was identified as the acetal **155** by NMR and IR analysis.



97



155

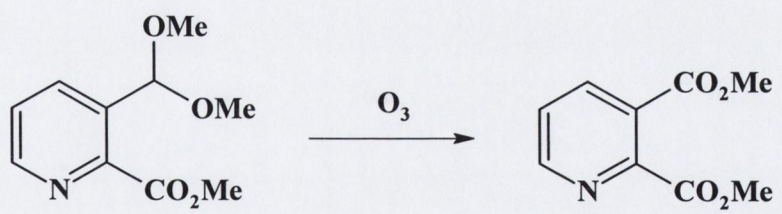
The infrared spectrum of the novel compound **155**, which was obtained as an oil, shows a strong absorption at 1735 cm^{-1} which suggests the presence of a carboxyl ester function and a group of signals between 1000 and 1200 cm^{-1} where aliphatic ether bonds absorb.

The most downfield signal observed in the proton NMR spectrum of the by-product **155** is evident as a 1H-doublet (J 4.0 Hz) at δ_H 8.62 ppm and is assigned to the *C*-6 proton. One of the two 1H-double doublets resonates at δ_H 8.06 ppm (J_1 8.0 Hz, J_2 1.5 Hz, *H*-4), the other appears at δ_H 7.44 ppm (J_1 8.0 Hz, J_2 4.8 Hz, *H*-5). A 1H-singlet at δ_H 6.00 ppm is unambiguously assigned to the methine proton, while a singlet at δ_H 3.97 ppm, with an integration value of three, corresponds to the methyl ester group protons. The last signal, a 6H-singlet, which is due to the H's of the methoxy groups, is found at δ_H 3.36 ppm. The ^{13}C NMR spectrum of **155** shows a resonance for the carbon of the carbonyl group at δ_C 165.95 ppm and one for the methine carbon at δ_C 99.32 ppm. The CH_3-groups of the methyl ester and methoxy groups are evident at δ_C 52.30 and 53.63 ppm, respectively. The signals due to the remaining pyridine carbons are listed in **Table 2.2**.

Table 2.2: Chemical shifts δ_C of the acetal **155**.

Assignment	Chemical Shift δ_C (ppm)
$CO_2\underline{C}H_3$	52.30
$O\underline{C}H_3$	53.63
$\underline{C}H(OCH_3)_2$	99.32
C-5	125.15
C-3	134.29
C-4	135.51
C-2	147.17
C-6	148.21
$\underline{C}O_2CH_3$	165.95

Several more ozonolyses were carried out in which the reaction conditions were further optimised and "cleaner" product mixtures were obtained. It was also shown that methanol is a superior solvent to ethyl acetate, and that dimethyl sulfide reduces the hydroperoxidic intermediates more rapidly and more efficiently than triethylamine. In fact, when triethylamine was employed, only very small amounts of the desired aldehydo ester **106** were found in the reaction mixture. Additionally, the formation of the dimethyl ester **156** was observed, a compound which might have arisen from the acetal **155** by the action of ozone (**Scheme 2.9**).[88]

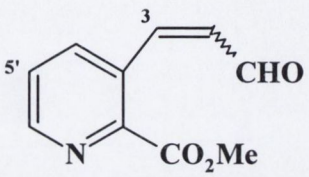


155 **156**

Scheme 2.9: Formation of the dimethyl ester **156**.

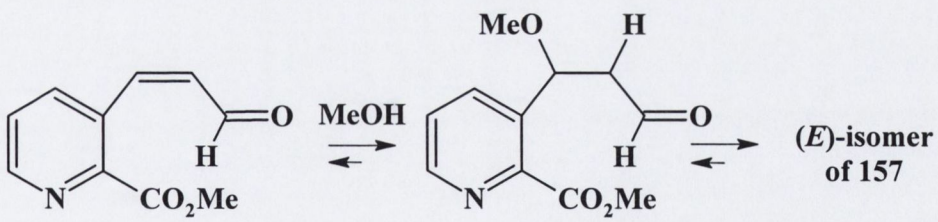
The NMR and IR data as well as the melting point obtained for compound **156** agree favourably with those reported in the literature.[89]

On one occasion the ozonolysis of 8-methoxyquinoline **105** in methanol was stopped before the required amount of ozone had been passed into the solution. ^{1}H NMR spectral analysis of the product mixture after the usual reductive work-up showed that, beside the aldehydo ester **106**, the (*E*)- and (*Z*)-isomers of the unsaturated aldehyde **157** had also been formed. Column chromatography of the crude product mixture was employed to separate the two isomers from the aldehyde **106** and unreacted 8-methoxyquinoline **105**. Another very small fraction contained an unidentified aldehyde.



157

As evidenced by NMR spectroscopy, the crude oil after the reduction process contained both isomers of **157**, although after cleavage of the 7,8-bond of the quinoline **105** only the (*Z*)-isomer should be expected. However, when the separation of the two unsaturated aldehydes **157** was attempted, it was found that during the isolation/purification procedure the (*Z*)-isomer was converted completely into the aldehyde **157** with the (*E*)-configured double bond. This conversion possibly proceeded *via* a reversible attack at the *C*-3 carbon by a nucleophile, for example, methanol, yielding the intermediate **158**, which, after rotation around the (MeO)C-C(CHO)-axis, then eliminated methanol again to give the sterically favoured (*E*)-isomer (**Scheme 2.10**).



157 **158**

Scheme 2.10: Isomerisation of the aldehyde **157** *via* reversible nucleophilic attack.

The unidentified compound obtained during column chromatography might have been the intermediate **158**. However, this could not definitely be confirmed due to the very small amount of this fraction, which also contained a few more (aliphatic) compounds causing difficulties with the interpretation of the proton NMR spectrum.

As has been mentioned above, the unstable (*Z*)-isomer of the aldehyde **157** could not be fully analysed, but the proton NMR spectrum of the mixture provides rather firm evidence for its existence. The aldehyde proton appears as a 1H-doublet (*J* 8.5 Hz) at δ_H 9.62 ppm and a 3H-singlet at δ_H 3.96 ppm corresponds to the methyl ester protons. The vinylic H's are represented by a doublet at δ_H 8.08 ppm (*J* 11.5 Hz, *H*-3) and a double doublet at δ_H 6.26 ppm (J_1 11.8 Hz, J_2 8 Hz, *H*-2) and the coupling constants of both signals show the expected values.[87] The remaining pyridine protons can be assigned to the resonances at δ_H 8.75, 7.72 and 7.52 ppm, exhibiting the predicted multiplicities and coupling constants.

The (*E*)-isomer of **157** was isolated as a white solid. After purification, its structure was determined by IR and NMR spectroscopy as well as high resolution mass spectrometry (HRMS). The infrared spectrum of **157** confirms the presence of two carbonyl groups (overlapping C=O absorptions at ~1710 cm^{-1}) and the calculated *m/z* matches the experimental data perfectly. A doublet at δ_H 8.38 ppm (*J* 16 Hz, *H*-3) and a double doublet at δ_H 6.65 ppm (J_1 16 Hz, J_2 7.5 Hz, *H*-2) in the ^1H NMR spectrum can undoubtedly be assigned to the vinylic protons. The corresponding carbons, *C*-2 and *C*-3, resonate at δ_C 132.07 and 150.21 ppm, respectively.

Table 2.3: Chemical shifts δ_C of the (*E*)-isomer of the unsaturated aldehyde **157**.

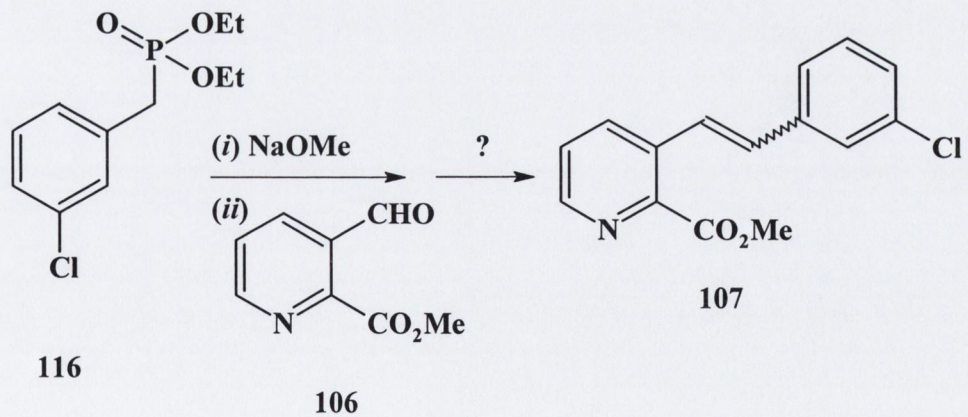
Assignment	Chemical Shift δ_C (ppm)	Assignment	Chemical Shift δ_C (ppm)
CO_2CH_3	52.82	*C*-2'	145.86
C-5'	126.29	*C*-6'	147.59
C-3'	131.51	*C*-3	150.21
C-2	132.07	CO_2CH_3	165.26
C-4'	135.50	*C*-1	192.87

The occurrence of the unsaturated aldehyde **157** is not unexpected, proving that the electron-richest bond 7-8 of the aromatic system is attacked by ozone first. Similar partial ozonolysis reactions of naphthalene have been reported.[90,91]

In summary, the ozonolysis of 8-methoxyquinoline **105** at room- or ice bath temperature followed by a reductive work-up was successful, and crude 3-formyl-2-carbomethoxypyridine **106** was obtained in good yields. However, the isolation procedures thus far are still lacking of efficiency, which is due to the poor (thermal) stability of the aldehyde **106** and to the difficulty in separation of by-products. Hot extractions of the crude, thick oils with petrol ether, for example, yielded good results with regard to the purity of the desired carbonyl compound **106**, but this process was not very efficient and the elevated temperature probably enhanced the occurrence of side-reactions, which led to very small amounts of pure isolated material.

2.3.3 Horner-Emmons reaction of the aldehyde 106

The second most important reaction in this synthetic route was the olefination of the aldehydo-ester **106**. As has been said above, an inexpensive Horner-Emmons reaction would clearly be preferred, however, when the aldehyde **106** was added to the deprotonated benzylphosphonate **116** in DMF solution (**Scheme 2.11**), a complex mixture of compounds was obtained.



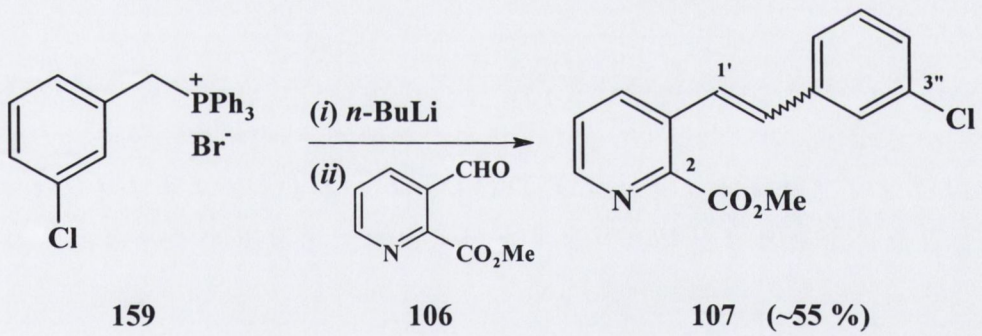
116 **106** **107**

Scheme 2.11: Horner-Emmons reaction of the aldehyde **106**.

The NMR spectra could not give firm evidence for the formation of the desired stilbazole **107** and facile separation of the contents of the mixture was not possible. The occurrence of a side-reaction, which is discussed in **Section 1.8 (p41)**, or steric hindrances between the carboxyl ester and phosphonate ester groups might be an explanation for the unsatisfactorily outcome of this reaction.

2.3.4 Wittig reaction of the aldehyde 106

For the Wittig reaction[92] of the aldehydo-ester **106** mostly the crude oils obtained from the work-up of the ozonolyses of 8-methoxyquinoline **105** were used. The Wittig reagent, triphenylphosphonium bromide **159**,[93] was prepared *via* the addition of *m*-chlorobenzyl bromide to a toluene solution of triphenyl phosphine. The phosphonium salt **159** was isolated from this mixture and then used in the olefination where it was dissolved in THF and deprotonated with one molar equivalent of *n*-butyllithium. The addition of the aldehyde **106** to this mixture at –78 °C afforded the stilbazole **107** as a mixture of its (*E*)- and (*Z*)-isomers in moderate yield (~55 %) (**Scheme 2.12**).



159 **106** **107 (~55 %)**

Scheme 2.12: Wittig-reaction of the aldehyde **106** to give the stilbazole **107**.

The two isomers of **107** were separated by column chromatography which afforded each isomer as white crystals and their structure was established by standard analysis procedures, *i.e.*, IR, NMR and HRMS. A characteristic absorption in the IR spectrum of the (*Z*)-configured stilbazole **107** at 1718 cm^{-1} indicates the presence of an ester C=O bond. The ^1H NMR experiment shows a 3H-singlet at δ_H 3.90 ppm, which is assigned to the methyl ester protons, and a 1H-doublet at δ_H 6.61 ppm with a coupling constant *J* of 12.0 Hz which is due to the vinyl proton *H*-2'.

Another doublet (*J* 7.5 Hz) at δ_H 6.81 ppm corresponds to *H*-4" of the benzene ring. The next signal is a 3H-multiplet at δ_H 6.95-7.01 ppm, which is produced by the other vinylic proton *H*-1' and by *H*-2" and *H*-5" of the benzene ring. The signal assigned to the remaining phenyl proton *H*-6" appears as a doublet at δ_H 7.04 ppm, which has a coupling constant of 8.0 Hz. Three 1H-signals at δ_H 7.17, 7.43 and 8.52 ppm correspond to the pyridine protons. The assignment of the ^{13}C NMR spectrum was assisted by DEPT- and C-H COSY experiments (**Table 2.4**).

Table 2.4: Chemical shifts δ_C of the (*Z*)-isomer of the stilbazole **107**.

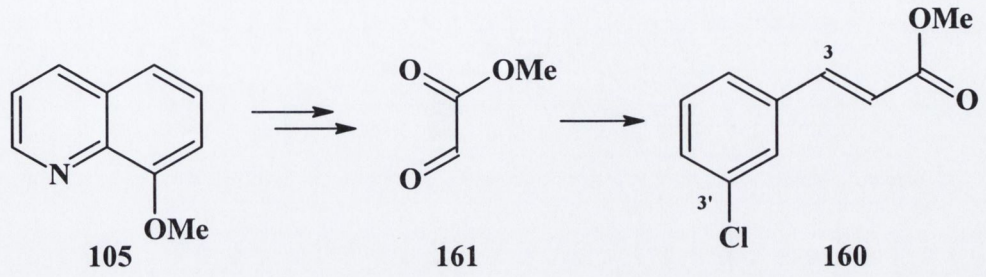
Assignment	Chemical Shift δ_C (ppm)	Assignment	Chemical Shift δ_C (ppm)
CO_2CH_3	52.21	*C*-3, *C*-3"	133.66, 134.21
C-5	125.30	*C*-1"	137.31
C-4"	126.75	*C*-4	138.75
C-6"	126.93	*C*-2	145.88
C-1, *C*-2", *C*-5"	128.07, 128.52, 129.01	*C*-6	147.84
C-2'	129.61	CO_2CH_3	165.41

Similar data was obtained for the (*E*)-isomer of the Wittig-product **107**. The IR spectrum shows a strong band at 1730 cm^{-1} due to the ester function and in a ^1H NMR experiment two 1H-doublets, *H*-2' at δ_H 6.86 and *H*-1' at δ_H 7.82 ppm, confirm the presence of a vinyl group, this time with an (*E*)-configuration.

Table 2.5: Chemical shifts δ_C of the (*E*)-isomer of the stilbazole **107**.

Assignment	Chemical Shift δ_C (ppm)	Assignment	Chemical Shift δ_C (ppm)
CO_2CH_3	52.42	*C*-3, *C*-3"	133.96, 134.15
C-6"	124.65	*C*-4	134.37
C-1'	125.31	*C*-1"	138.01
C-5, *C*-2"	125.89, 126.31	*C*-2	145.01
C-4"	127.78	*C*-6	147.71
C-5"	129.46	CO_2CH_3	165.74
C-2'	131.33		

In some cases when the unpurified aldehyde **106** was used for the Wittig reaction, column chromatography of the crude product mixture afforded a minor fraction which contained (*E*)-3-(3'-chlorophenyl)prop-2-enoate **160**. The precursor to this compound must be methyl glyoxylate **161**,[94] which has possibly arisen from a scission product during the ozonolysis of 8-methoxyquinoline **105** (**Scheme 2.13**).

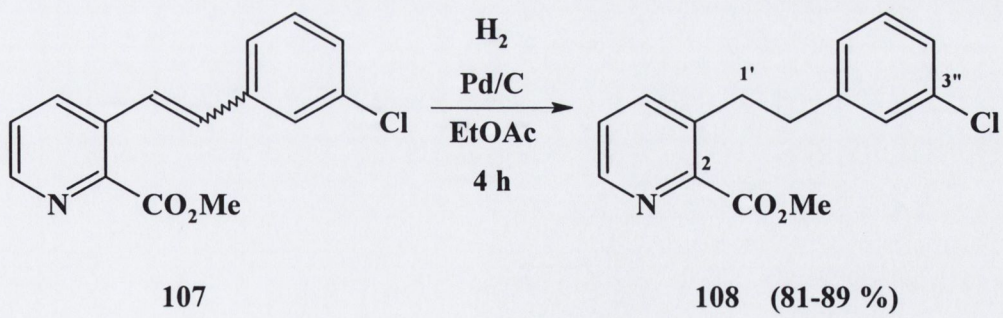


Scheme 2.13: Possible reaction pathway leading to the unsaturated ester **160**.

The analytical data for the low-melting solid **160** (*lit.* m. p. 45-46 °C) was identical to that reported in the literature.[95]

2.3.5 Hydrogenation of the stilbazole 107

Hydrogenation of the unsaturated methyl ester **107** at atmospheric pressure, carried out in ethyl acetate and with palladium on activated charcoal as the catalyst (**Scheme 2.14**), was straightforward and the novel phenethylpyridine **108** was obtained as white crystals in 81-89 % of the theoretical yields after recrystallisation.



107 **108 (81-89 %)**

Scheme 2.14: Hydrogenation of the stilbazole **107** to give the ester **108**.

The infrared spectrum of the diarylethane **108** shows an absorption corresponding to the ester group at 1726 cm^{-1}. The signal due to the protons of this group appears in the NMR spectrum as a 3H-singlet at δ_H 4.02 ppm. The resonances corresponding to the methylene protons are evident at δ_H 2.94 and 3.25 ppm, however, these two signals did not appear as triplets as might have been expected, but as multiplets. This observation might be explained with restricted rotational freedom due to the methyl ester group. A double doublet at δ_H 7.38 ppm (J_1 7.8 Hz and J_2 4.8 Hz) is assigned to *H*-5 of the pyridine ring. The protons *H*-4 and *H*-6 also resonate in the form of double doublets, the first-mentioned at δ_H 7.54 ppm (J_1 8.0 Hz and J_2 1.5 Hz) and the other at δ_H 8.61 ppm (J_1 4.5 Hz and J_2 1.5 Hz). A 3H-multiplet at δ_H 7.18-7.26 ppm is due to three protons of the phenyl fragment, namely *H*-2", *H*-4" and *H*-5". The last proton, *H*-6", is represented by a double doublet (J_1 6.5 Hz and J_2 2.0 Hz) at δ_H 7.07 ppm.

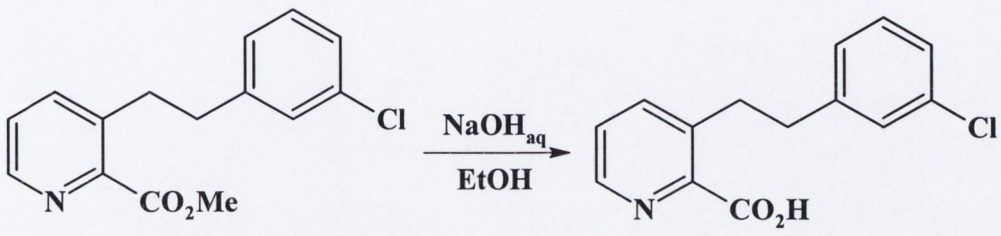
Table 2.6 shows the assignments in the carbon NMR spectrum of the ester **108**, the most important features of which are the signals at δ_C 34.55 and δ_C 36.61 ppm corresponding to *C*-1' and *C*-2' of the ethylene bridge.

Table 2.6: Chemical shifts δ_C of the diarylethane **108**.

Assignment	Chemical Shift δ_C (ppm)	Assignment	Chemical Shift δ_C (ppm)
C-1'	34.55	*C*-3	138.18
C-2'	36.61	*C*-4	139.12
CO_2CH_3	52.37	*C*-1"	142.58
C-5	125.68	*C*-2	146.38
C-2", *C*-4",	125.93, 126.39,	*C*-6	146.88
C-5", *C*-6"	128.24, 129.23	CO_2CH_3	165.79
C-3"	133.70		

2.3.6 Saponification of the ester 108

The last step in this synthetic route is the hydrolysis of the ester **108** (**Scheme 2.15**), from which the target compound, 3-[2'-(*m*-chlorophenyl)ethyl]picolinic acid **45**, was obtained in ~90 % yield after recrystallisation.



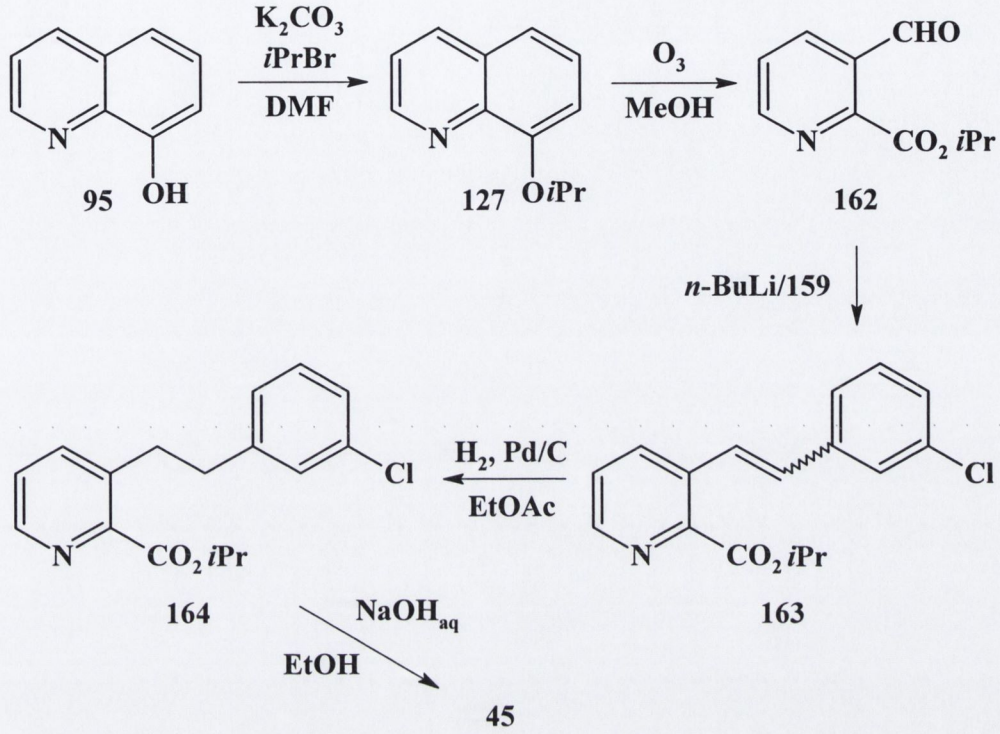
108 **45 (~90 %)**

Scheme 2.15: Saponification of the ester **108** to give the pivotal acid **45**.

Although it is a known compound, the melting point of the acid **45** does not appear to have been reported in either the academic or patent literature. However, the NMR, IR and HRMS data of the purified material provide enough evidence for the successful conversion of the ester **108** into the acid **45**. For example, in the IR spectrum of **45**, an absorption corresponding to the C=O bond of the carboxyl group of derivative **45** occurs at 1658 cm^{-1} which is significantly lower than the wavelength of the IR band due to the ester function of compound **108**. In the HRMS spectrum an *m/z* signal of 262.0620 is observed which matches the calculated *m/z* (262.0635) for $C_{14}H_{12}ClNO_2+H^+$ sufficiently and the proton NMR spectrum also shows the expected[38] resonances.

2.4 Second synthetic approach towards the picolinic acid 45

As has been mentioned above, the second synthetic route towards the acid **45** (**Scheme 2.16**) was very similar to the one described in the previous sections.



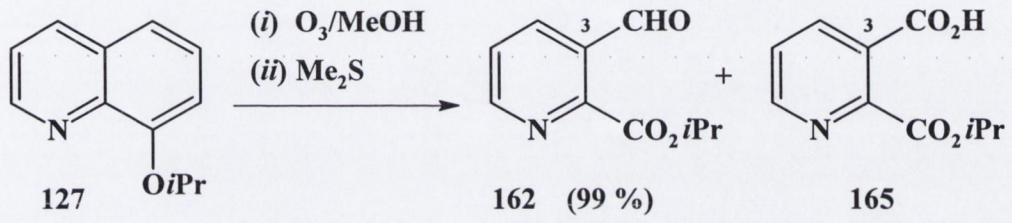
Scheme 2.16: Synthetic route towards the acid **45** *via* 8-isopropoxyquinoline **127**.

2.4.1 Preparation of 8-isopropoxyquinoline 127

This second pathway was much more efficient than the synthetic route to prepare the methyl ether and esters, respectively. For example, 8-isopropoxyquinoline **127** was synthesised following a literature procedure[96] reported by Gilchrist and Rahman: a DMF solution of 8-hydroxyquinoline **95** was treated with a two-fold excess of potassium bicarbonate and 2-bromopropane (**Scheme 2.16**). From this, the target compound **127** was obtained in 85 % yield and in excellent purity after a facile work-up. This improvement to the alkylation described in **Scheme 2.7 (p56)** is probably due to no or only little *N*-alkylation which is the major side-reaction in the preparation of the methyl ether **105**. The results obtained from IR and ^{1}H NMR analysis of the ether **127** matched the experimental data reported in the literature.[97]

2.4.2 Ozonolysis of 8-isopropoxyquinoline 127

8-Isopropoxyquinoline **127** was then subjected to ozone using the same conditions that were employed in the ozonolyses of 8-methoxyquinoline **105**. Ozonisation in methanol at 0 °C was followed by the addition of dimethyl sulfide and this afforded the desired aldehydo ester **162** in very good yields of up to 99 % of crude product. The oils obtained after the reductive work-up contained fewer impurities, of which the major one was the corresponding carboxylic acid **165**. The proton NMR spectrum of crude product, obtained from one of the reactions shown in **Scheme 2.17**, is depicted in **Figure 2.1**.



Scheme 2.17: Ozonolysis of 8-isopropoxyquinoline **127**.

The spectroscopic data of the aldehyde **162** matched the analytical results for the same compound **162** reported by Ornstein and co-workers.[98]

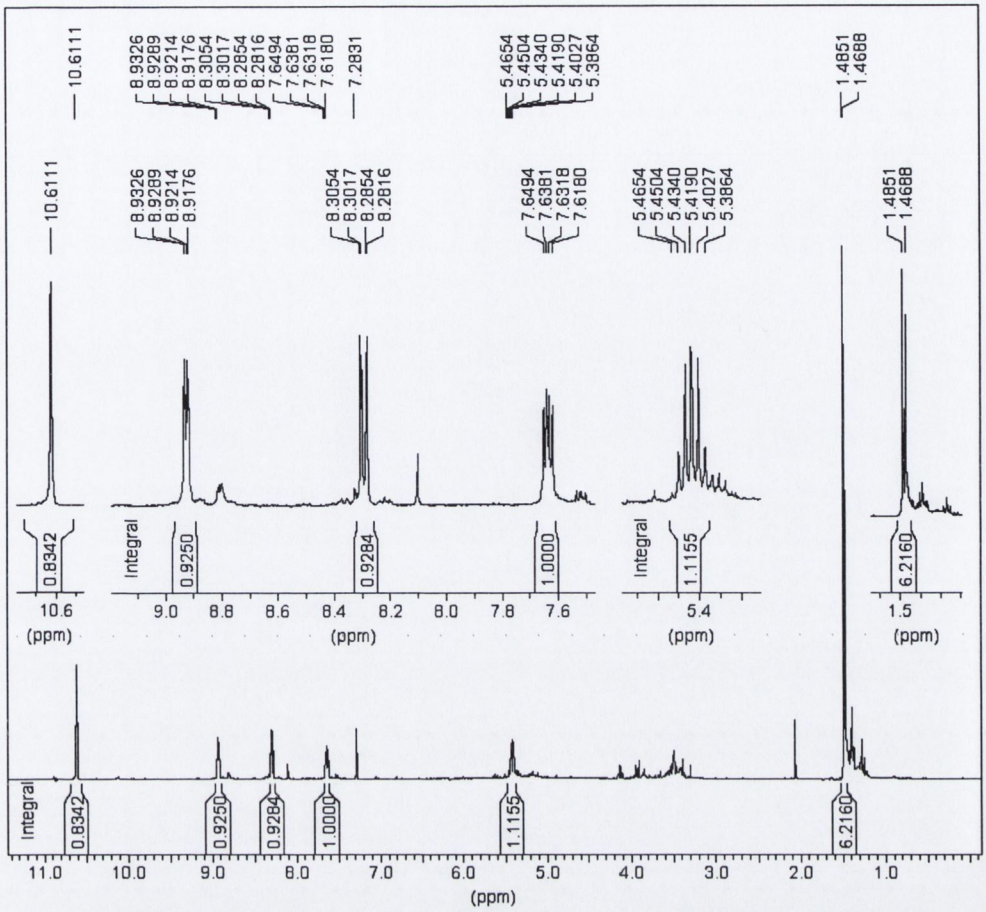
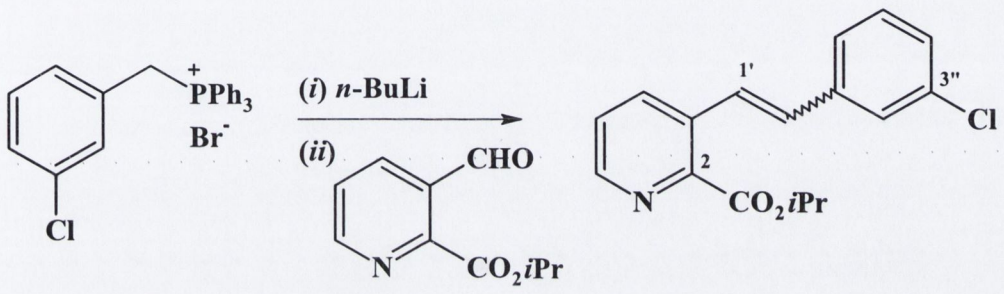


Figure 2.1: ^{1}H NMR spectrum of an ozonolysis mixture of 8-isopropyl-quinoline **127** after a reductive work-up.

In the spectrum shown above, the aldehyde proton of the isopropyl ester **162** is represented by the 1H-singlet at δ_H 10.61 ppm. The set of three double doublets at δ_H 8.93, 8.29 and 7.63 ppm is due to the pyridine protons of compound **162**. Another set of three much smaller signals, one of them partially hidden by *H*-4 of **162** at δ_H 8.29 ppm, corresponds most likely to *H*-4, *H*-5 and *H*-6 of the acid **165**. The peak at δ_H 7.28 ppm is due to residual chloroform in the deuterated solvent $CDCl_3$, however, the source of the singlet at δ_H 8.10 ppm could not be identified. The aliphatic region shows a 1H-multiplet (septet) and a 6H-doublet which can be assigned unambiguously to the isopropyl group of the aldehyde **162**. The remaining resonances may be ascribed to aliphatic scission products of the ozonolysis, extraction solvent (ethyl acetate) and the isopropyl group of the by-product **165**.

2.4.3 Olefination of 3-formyl-2-carboisopropoxypyridine 162

Although the isopropyl ester **162** was obtained in higher yields and with fewer by-products than the methyl ester **106**, the first-mentioned compound is still susceptible to oxidation, which makes it difficult to purify. Thus, again the crude oils obtained from the ozonolysis of 8-isopropoxyquinoline **127** were used directly in the Wittig reaction. Addition of the aldehyde **162** to a THF solution which contained the ylid of the phosphonium salt **159** afforded the stilbazole **163** as a mixture of its geometrical isomers (**Scheme 2.18**).



159 **162** **163 (44 %)**

Scheme 2.18: Wittig reaction of the aldehydo ester **162**.

This compound **163** was isolated by column chromatography (total yield: 44 %) and then analysed. The IR spectra of the (*E*)- and (*Z*)-isomers of **163** show absorptions at 1712 and 1716 cm^{-1}, respectively, corresponding to their carbonyl groups and the *m/z*-signals obtained from HRMS analysis of the isomers had the expected values, thus, providing further evidence for the success of this reaction. In the proton NMR spectrum of the *cis*-configured ester **163** a 1H doublet at δ_H 6.67 ppm with *J* 12.4 Hz is due to the *H*-2' proton and in a TOCSY 2D experiment this signal shows coupling to another 1H-doublet at δ_H 7.02 ppm with the same *J*-value which must correspond to *H*-1'. The protons of the isopropyl group resonate at δ_H 1.41 and 5.31 ppm, respectively. In the aromatic region a 1H-double doublet (J_1 4.4 Hz and J_2 1.5 Hz) at δ_H 8.61 ppm is assigned to *H*-6 of the pyridine ring. The other two pyridine protons also appear as double doublets, one at δ_H 7.49 ppm (J_1 8.0 Hz and J_2 1.5 Hz, *H*-4) and the other at δ_H 7.22 ppm (J_1 7.7 Hz and J_2 4.8 Hz, *H*-5). A 1H-doublet at δ_H 6.89 ppm has a coupling constant of 7.3 Hz and this signal is assigned to *H*-4" of the phenyl ring.

The remaining resonances are a 2H-multiplet at δ_H 7.04-7.09 ppm, corresponding to *H*-2" and *H*-5", and a 1H-double doublet at δ_H 7.12 ppm (J_1 8.0 Hz and J_2 1.4 Hz) due to *H*-6". The carbon signals of the (*Z*)-isomer of **163** (**Table 2.7**) were assigned using C-H COSY, HMBC and DEPT experiments.

Table 2.7: Chemical shifts δ_C of the (*Z*)-isomer of the stilbazole **163**.

Assignment	Chemical Shift δ_C (ppm)	Assignment	Chemical Shift δ_C (ppm)
CH_3	21.35	*C*-2'	129.40
$CH(CH_3)_2$	69.29	*C*-3, *C*-3"	133.71, 133.76
C-5	125.02	*C*-1"	137.37
C-4"	126.82	*C*-4	138.65
C-6"	126.98	*C*-2	146.99
C-1', *C*-2", *C*-5"	128.30, 128.59, 129.07	*C*-6	148.04
		CO_2CH	164.91

In the ^{1}H NMR spectrum of the *trans*-isomer of **163**, the vinylic protons *H*-1' and *H*-2' can be assigned to the doublets at δ_H 7.82 ppm and δ_H 7.01 ppm, respectively, both exhibiting a coupling constant of *J* 16.4 Hz, which is expected.[87] The chemical shifts of the methyl and methine protons of the isopropyl ester group are very similar to those of the (*Z*)-isomer.

Table 2.8: Chemical shifts δ_C of the (*E*)-isomer of the stilbazole **163**.

Assignment	Chemical Shift δ_C (ppm)	Assignment	Chemical Shift δ_C (ppm)
CH_3	21.43	*C*-3	133.56
$CH(CH_3)_2$	69.69	*C*-3"	134.34
C-6"	124.65	*C*-4	134.89
C-1'	125.22	*C*-1"	138.01
C-5	125.62	*C*-2	147.45
C-2"	126.38	*C*-6	147.51
C-4", *C*-5"	127.96, 129.58	CO_2CH	164.80
C-2'	131.50		

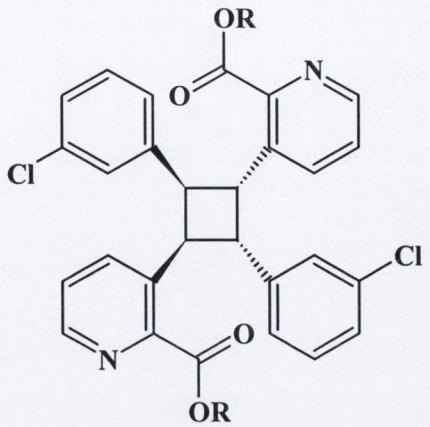
The pyridine protons resonate as doublets and double doublets at δ_H 7.51, 8.10 and 8.69 ppm. Three signals are observed for the phenyl H's: a 1H-doublet with a coupling constant of 6.8 Hz at δ_H 7.43 ppm for *H*-6", a 1H-singlet at δ_H 7.54 ppm corresponding to *H*-2" and a 2H-multiplet at δ_H 7.26-7.37 ppm which is assigned to *H*-4" and *H*-5". The data obtained from carbon NMR experiments is shown in **Table 2.8**.

Column chromatography of the Wittig reaction mixture afforded a small fraction of another product. High-resolution mass spectrometry revealed that this has the molecular formula $C_{34}H_{32}Cl_2N_2O_4$, and from the isotopic peaks due to chlorine it was deduced that this new compound could be the dimer of the stilbazole **163**. The ^{1}H NMR spectrum of this by-product exhibits the expected aryl, heteroaryl and isopropyl ester resonances. Signals for two methine protons appear as double doublets at δ_H 4.66 and 5.15 ppm, each with J_1 10.0 Hz and J_2 8.0 Hz. In the non-decoupled ^{13}C NMR spectrum of **166a**, two doublets with a coupling constant of $^1J_{C\text{-}H}$ 141.0 Hz resonate at δ_C 43.25 and 45.41 ppm. These chemical shifts and *J*-values[87,99] are suggestive of the presence of a cyclobutane ring, and this data allows the structure **166a** to be assigned to this unexpected product. The following table provides the chemical shifts δ_C observed in the carbon NMR spectrum and their assignments.

Table 2.9: Chemical shifts δ_C of the cyclobutane **166a**.

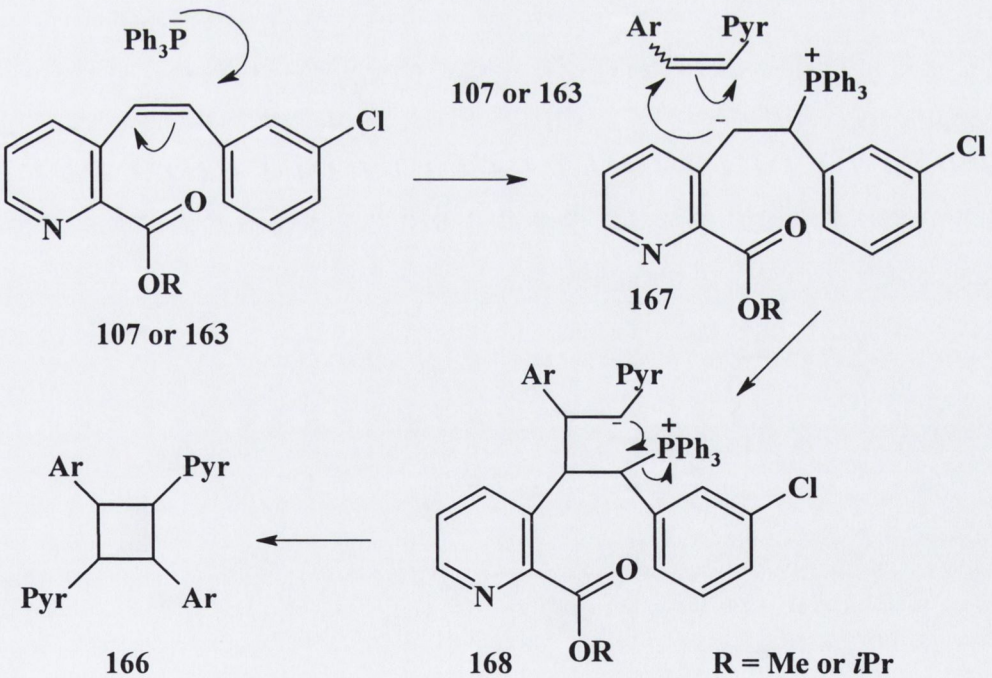
Assignment	Chemical Shift δ_C (ppm)	Assignment	Chemical Shift δ_C (ppm)
CH_3	21.24, 21.31	*C*-4' or *C*-5'	129.09
C-2, *C*-4	43.25	*C*-3'	133.69
C-3, *C*-5	45.41	*C*-4"	135.85
$CH(CH_3)_2$	69.38	*C*-3"	136.14
C-5"	125.43	*C*-1'	140.67
C-6'	125.73	*C*-6"	146.71
C-4' or *C*-5'	126.48	*C*-2"	146.98
C-2'	127.89	CO_2CH	165.04

The dimer **166a** was obtained as white, low-melting crystals that have a melting point of 40-42 °C and show an absorption at 1718 cm^{-1} in the IR spectrum.



166a R = *i*-Pr
166b R = Me

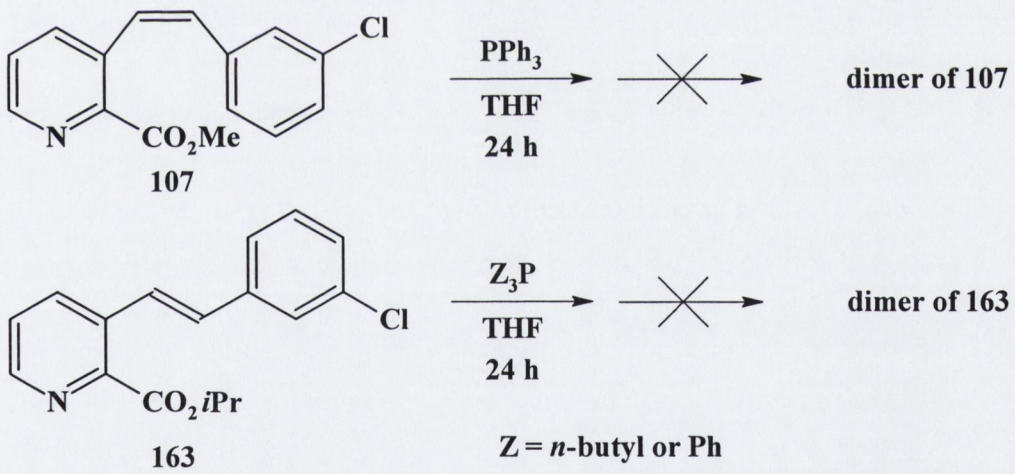
When this compound had been identified as the cyclobutane **166a**, the stereochemistry of which will be discussed later, the spectra of the Wittig reaction mixtures of the methyl ester aldehyde **106** were re-examined and indeed, a very small amount of a product, which must have been the methyl ester derivative **166b**, was found. The first attempt to explain the formation of these unexpected by-products was based on the assumption that cyclisation might have been induced by nucleophilic attack of triphenylphosphine according to **Scheme 2.19**.



Scheme 2.19: Possible mechanism leading to formation of the cyclobutanes **166**.

The addition of triphenylphosphine, which might have been carried over from the preparation of the Wittig reagent **159**, to the *C*-2' carbon of the stilbazole **107** or **163**, respectively, gives the zwitterion **167**. The latter might then be attacked by another molecule of the unsaturated ester **107** or **163**, which yields the intermediate **168**. Finally, triphenylphosphine is expelled and the cyclobutane **166** is formed. This type of reaction is already known and tertiary phosphines have been used[100] in catalytic amounts to dimerise/oligomerise acrylonitriles.

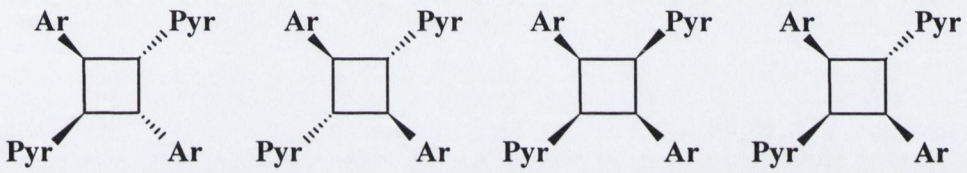
To examine if the present reaction proceeded *via* this mechanism, an experiment was conducted in which the (*Z*)-isomer of the methyl ester stilbazole **107** was dissolved in THF and a catalytic amount of triphenylphosphine was added. After stirring this mixture for 24 hours it was analysed by ^{1}H NMR spectroscopy, but none of the dimer **166b** had formed. In a second experiment the (*E*)-isomer of the ester **163** was subjected to the same process, but again, the unsaturated compound remained unchanged. Yet another unsuccessful reaction was carried out in which the far more reactive tri-*n*-butylphosphine was added to a THF solution of the (*E*)-isomer of the stilbazole **163** (**Scheme 2.20**).



Scheme 2.20: Attempted phosphine-catalysed cyclisations of the stilbazoles **107** and **163**.

A second rationale to explain the formation of **166** is photodimerisation[101] of the unsaturated esters **107** and **163**, respectively, which might have occurred during column chromatography of the Wittig reaction mixtures. Unfortunately, due to time-restraints no further investigations could be carried out to test this hypothesis.

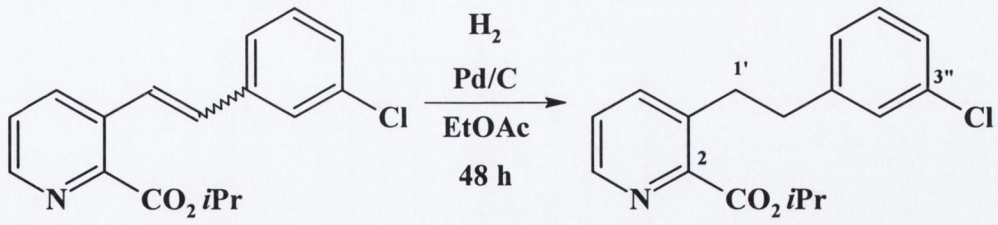
The geometry and stereochemistry of the cyclobutanes **166** was established as follows. If these compounds **166** are formed *via* an ionic mechanism like the one shown in **Scheme 2.19 (p74)**, a head-head structure can be excluded, as it is highly unlikely that the zwitterion **167** will attack a second molecule of the stilbazole at the less electrophilic methine carbon next to the pyridine ring. It has been shown[101] that in photodimerisation reactions of similar stilbazoles the formation of head-tail structures is also much more preferred, and thus an alternating arrangement of pyridine and benzene rings at the cyclobutane ring of **166** has been proposed. The stereochemistry can be deduced from the shape of the two signals produced by the aliphatic ring protons in the ^{1}H NMR spectrum. Symmetry arguments preclude the alternative structures B and C where the cyclobutyl methine protons should appear as triplets, and also eliminate structure D where the cyclobutyl protons would be in a 2:1:1 integrated ratio. Hence, it must be assumed that structure A represents the actual configuration of the dimer **166**.



The formation of the cyclobutane **166** is the major drawback of this synthetic route. However, this by-product was only formed in small amounts and can be separated by column chromatography.

2.4.4 Hydrogenation of the stilbazole 163

Hydrogenation of a mixture of the (*E*)- and (*Z*)-isomers of the stilbazole **163** (**Scheme 2.21**) was conducted using the same reaction conditions that were employed in the reduction of the corresponding methyl ester **107** (*cf.* **Scheme 2.14, p65**).



163 **164 (91 %)**

Scheme 2.21: Hydrogenation of the stilbazole **163** at atmospheric pressure.

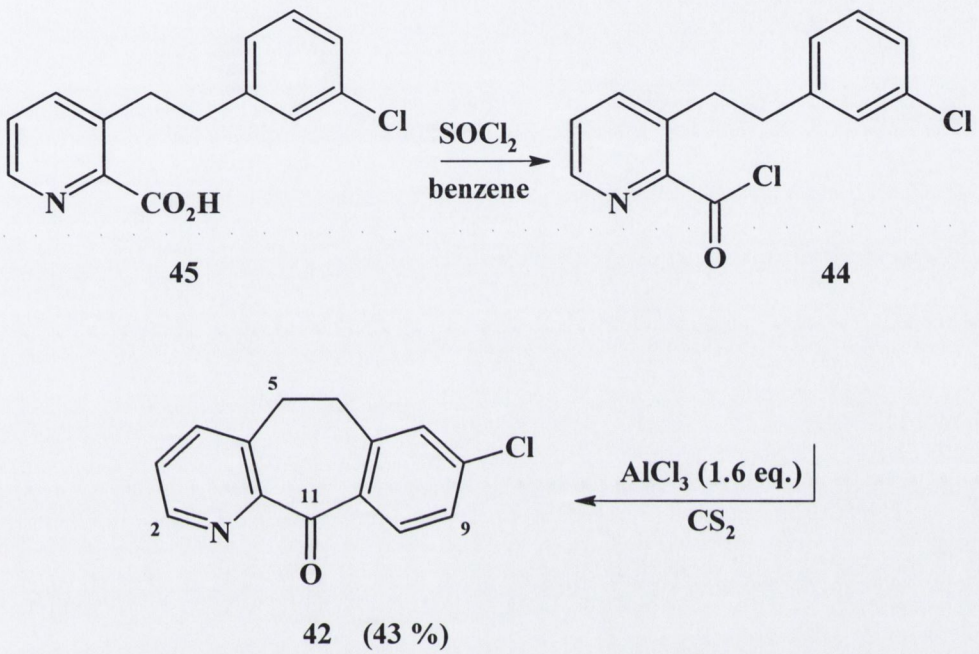
Completion of this reaction took several hours longer than the hydrogenation of the stilbazole **107**, however, in the end the expected saturated isopropyl ester **164** was obtained in excellent yield (91 %). Unfortunately, the oily solid could not be satisfactorily recrystallised, but the IR and NMR spectra of the hydrogenated isopropyl ester **164**, which are very similar to that of the methyl compound **108**, confirmed the success of this reaction. For example, infrared analysis of compound **164** produced an absorption at 1722 cm^{-1} (Me-ester: 1726 cm^{-1}) and in the ^1H NMR spectrum the methylene protons *H*-2' and *H*-1' resonate at δ_H 2.94 and 3.19 ppm (Me-ester: δ_H 2.94 and 3.25 ppm), respectively. **Table 2.10** provides all other chemical shifts which were observed in the carbon NMR spectrum. In the last step of this route, the isopropyl ester was deprotected by means of sodium hydroxide. Recrystallisation of the crude product afforded the acid **45** in 90 % yield.

Table 2.10: Chemical shifts δ_C of the diarylethane **164**.

Assignment	Chemical Shift δ_C (ppm)	Assignment	Chemical Shift δ_C (ppm)
*C*H$_3$	21.37	*C*-3"	133.72
C-1'	34.31	*C*-3	137.28
C-2'	36.53	*C*-4	139.29
*C*H(CH$_3$)$_2$	69.38	*C*-1"	142.48
C-5	125.28	*C*-6	146.59
C-2", *C*-4",	125.97, 126.31,	*C*-2	147.36
C-5", *C*-6"	128.19, 129.25	*C*O$_2$CH	164.97

2.5 Intramolecular cyclisation (Friedel-Crafts acylation) of the acid 45

Numerous synthetic approaches towards the tricyclic ketone **42** have been attempted (*cf.* **Section 1.52, p16**) and one of the earliest was also one of the most successful reactions. Here, Villani *et al.*[18] converted the pyridine derivative **45** into the acid chloride **44**, which was followed by an intramolecular Friedel-Crafts acylation to give the ketone **42** in 77 % yield (**Scheme 2.22**).



45 **44**

42 **(43 %)**

Scheme 2.22: Intramolecular Friedel-Crafts acylation of the acid chloride **44**.

According to the authors, the halogenation of the acid **45** was carried out in benzene and the cyclisation of **44** was conducted in carbon disulfide solution. The use of such toxic solvents prompted the author to try the cyclisation shown in **Scheme 2.22** in dichloromethane (DCM), a solvent which has been employed successfully in other Friedel-Crafts reactions.[102] Thus, the cyclisation of **45** was performed similarly to Villani's procedure with the exception that the diarylethane **45** was chlorinated with thionyl chloride and then cyclised in DCM solution. This procedure afforded the tricyclic ketone **42** in rather low yields (~43 %). However, this reaction has not been optimised and difficulties during the work-up prevented a more satisfactorily outcome.

2.6 Conclusions and future work

The target compound, the pivotal acid **45**, was prepared *via* two novel synthetic approaches. Most of the reactions employed in these syntheses were successful, however, optimisation of the ozonolyses of the alkoxyquinolines **105** and **127** and more efficient purification procedures of the resulting aldehydes are desirable and would obviously improve the overall yield of the entire process to make this synthetic route a valuable alternative to existing preparations of the acid **45**.

By using *n*-butyllithium in the Wittig reaction, the objective to employ less expensive reagents could not be fully met. However, preparation of the stilbazoles *via* this reaction was necessary, as attempted Horner-Emmons reaction of the aldehyde **106** failed. Besides steric hindrance, a recently discovered side-reaction by O'Neill,[60] discussed in **Section 1.8 (p41)**, might be an explanation for the unsuccessful Horner-Emmons reaction between the aldehyde **106** and the deprotonated phosphonate **116**. Further investigation of this facile and less expensive reaction might prove successful and would make this route even more attractive.

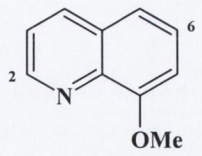
2.7 Experimental Section

General Conditions

Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded as solutions in $CDCl_3$ using a Bruker Avance DPX 400 MHz spectrometer. Coupling constants are recorded in Hz. Assignments were verified where appropriate by ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, DEPT and HMBC experiments. IR spectra were recorded as Nujol mulls (N) or liquid films (L) between sodium chloride plates using a Mattson FT-IR spectrometer. Mass spectra were obtained under electrospray conditions using a Micromass time-of-flight instrument. Melting points (uncorrected) were measured in unsealed capillary tubes using an Electrothermal IA9100 apparatus. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} 0.2 mm silica gel plates. Column chromatography was carried out using Merck Kieselgel 60 (70-230 mesh) silica gel. Ozonolysis was carried out using a BOC Mark 2 apparatus. THF solvent was dried over sodium metal and benzophenone and was freshly distilled before each use. Carbontetrachloride was stored over potassium hydroxide pellets and freshly distilled before each use. DMF solvent was stored over molecular sieves and distilled under vacuum before each use. All other solvents were used as received. Organic extracts of reaction products were dried over anhydrous magnesium sulfate.

8-Methoxyquinoline 105

8-Hydroxyquinoline **95** (4.60 g; 31.7 mmol) and anhydrous potassium carbonate (10.10 g; 73.1 mmol) in DMF (60 mL) were stirred under N_2 at 90 °C for 1 h after which time dimethyl sulfate (3 mL; 31.7 mmol) was added and the mixture was stirred for a further 2 h at 90 °C. The mixture was cooled to room temperature, diluted with water (300 mL) and extracted using dichloromethane. The combined organic layers were washed with aqueous potassium hydroxide solution (5 %; 100 mL) in portions, and then with water until the washings were no longer alkaline.

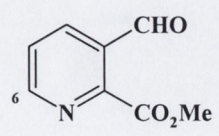


105

The extract was dried, filtered and the solvent removed by evaporation under reduced pressure to give *8-methoxyquinoline* **105** (2.67 g; 53 %), obtained as brown, oily crystals (*lit.*[81] m. p. 46-47 °C), ν_{max} (L) 3391, 3051, 3005, 2955, 2903, 2837, 1616, 1597, 1572, 1501, 1472, 1440, 1424, 1378, 1317, 1263, 1224, 1194, 1174, 1111, 1077, 1031, 994, 823, 792, 753 and 711 cm^{-1}, δ_H 4.07 (3H, s, OCH_3), 7.04 (1H, d, *J* 8.0, *H*-7), 7.35-7.50 (3H, m, *H*-3, *H*-5 and *H*-6), 8.11 (1H, dd, *J* 8.0 and 1.5, *H*-4) and 8.91 (1H, dd, *J* 4.2 and 1.8, *H*-2) ppm.

Ozonolysis of 8-methoxyquinoline 105: 3-formyl-2-carbomethoxypyridine 106

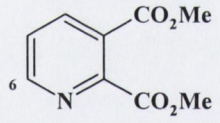
A three-necked flask (250 mL) fitted with a stirring bar and a dropping funnel was placed in an ice-bath and connected to the ozoniser. 8-Methoxyquinoline **105** (5.70 g; 35.8 mmol), dissolved in methanol (100 mL), was added and the solution was subjected to a stream of ozonised O_2 (containing ~1.5 % O_3) for 2 h (O_2-flow rate of 1 L/min). Ozone production was discontinued and the system was flushed with O_2 for 20 min to purge excess reagent. Dimethyl sulfide (6.6 mL; 90 mmol) was slowly added *via* the dropping funnel while the stirred mixture was continuously cooled in an ice-bath. After a further 30 min, solvents were removed under reduced pressure, the viscous brown oil obtained was taken up in ethyl acetate (100 mL) and the extract was washed with brine and dried.



106

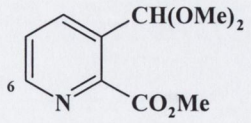
Evaporation of the solvent gave crude 3-formyl-2-carbomethoxypyridine **106** (4.80 g; 81 %) which could be used without further purification in the following Wittig reaction. An analytical sample of the aldehyde **106** was obtained by extracting the crude oily product using petroleum ether (b. p. 40-60 °C). *3-Formyl-2-carbomethoxypyridine* **106** crystallised out when the hot petroleum extracts were cooled to room temperature. This solid was recrystallised from petroleum ether to give analytically pure material as colourless needles, m. p. 82-83 °C, ν_{max} (N) 2953, 2924, 2854, 1710, 1693, 1578, 1460, 1426, 1377, 1318, 1263, 1196, 1177, 1088, 1056, 944, 850, 819, 801, 722 and 709 cm^{-1}, δ_H (DMSO-d_6) 3.94 (3H, s, CO_2CH_3), 7.81 (1H, dd, *J* 7.8 and 4.8, *H*-5), 8.31 (1H, dd, *J* 7.8 and 1.8, *H*-4), 8.87 (1H, dd, *J* 5.0 and 1.5, *H*-6) and 10.31 (1H, s, C*H*O) ppm, δ_C (100.6 MHz, DMSO-d_6) 52.95 (CO_2CH_3), 126.61 (*C*-5), 131.07 (*C*-3), 137.56 (*C*-4), 149.72 (*C*-2), 152.93 (*C*-6), 165.73 (CO_2CH_3) and 191.68 (CHO) ppm. HRMS : *m/z* 166.0502. *Calculated* for $[C_8H_7NO_3+H]^+$: 166.0504.

In some cases where ^1H NMR analysis of the crude product revealed significant amounts of impurities, the mixture was chromatographed (SiO_2/EtOAc/hexane). In this way, samples of the by-products **155** and **156** were isolated and characterised.



156

Dimethyl pyridine-2,3-dicarboxylate **156** had m. p. 54-56 °C (EtOAc) (*lit.*[89] m. p. 55-56 °C), ν_{max} (N) 3458, 3162, 3082, 3026, 3010, 2960, 2852, 1736, 1723, 1574, 1451, 1432, 1304, 1286, 1262, 1225, 1196, 1139, 1081, 1057, 958, 845, 782, 763 and 731 cm^{-1}, δ_H 3.94 (3H, s, CO_2CH_3), 4.00 (3H, s, CO_2CH_3), 7.50 (1H, dd, *J* 7.8 and 4.8, *H*-5), 8.18 (1H, dd, *J* 7.5 and 1.5, *H*-4) and 8.77 (1H, d, *J* 4.0, *H*-6) ppm.

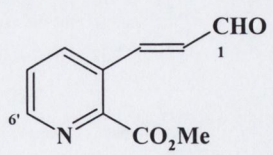


155

Methyl 3-(1',1'-dimethoxymethyl)pyridine-2-carboxylate **155** was obtained as an oil, ν_{max} (L) 3057, 2995, 2953, 2835, 1735, 1639, 1575, 1450, 1427, 1353, 1302, 1249, 1197, 1133, 1119, 1082, 984, 964, 909, 886, 834, 807, 759 and 712 cm^{-1}, δ_H 3.36 (6H, s, OCH_3 groups), 3.97 (3H, s, CO_2CH_3), 6.00 (1H, s, $CH(OCH_3)_2$), 7.44 (1H, dd, *J* 8.0 and 4.8, *H*-5), 8.06 (1H, dd, *J* 8.0 and 1.5, *H*-4) and 8.62 (1H, d, *J* 4.0, *H*-6) ppm, δ_C (100.6 MHz) 52.30 (CO_2CH_3), 53.63 ($CH(OCH_3)_2$), 99.32 ($CH(OCH_3)_2$), 125.15 (*C*-5), 134.29 (*C*-3), 135.51 (*C*-4), 147.17 (*C*-2), 148.21 (*C*-6) and 165.95 (CO_2CH_3) ppm. HRMS : *m/z* 212.0911. *Calculated* for $[C_{10}H_{13}NO_4+H]^+$: 212.0923.

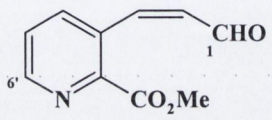
Interrupted ozonolysis of 8-methoxyquinoline 105: (*Z*)- and (*E*)-3-(2'-carbomethoxypyrid-3'-yl)prop-2-enal 157

A three-necked flask (250 mL) fitted with a stirring bar and a dropping funnel was placed in an ice-bath and connected to the ozoniser. 8-Methoxyquinoline **105** (7.09 g; 44.6 mmol), dissolved in methanol (100 mL), was added and the solution was subjected to a stream of ozonised O_2 (containing ~1.5 % O_3) for 3 h (O_2-flow rate of 0.5 L/min). Ozone production was discontinued and the system was flushed with O_2 for 20 min to purge excess reagent. Dimethyl sulfide (9 mL; 122.7 mmol) was slowly added *via* the dropping funnel while the stirred mixture was continuously cooled in an ice-bath. After a further 60 min, solvents were removed under reduced pressure, the viscous brown oil obtained was taken up in ethyl acetate (100 mL) and the extract was washed with brine and dried. Evaporation of solvent gave the crude product mixture as an oil (4.90 g) of which a portion (1.60 g) was chromatographed over silica gel using EtOAc/hexane as eluant.



(*E*)-157

One fraction (0.40 g) was rechromatographed using EtOAc/hexane to give pure (*E*)-*3-(2'-carbomethoxypyrid-3'-yl)prop-2-enal* **(*E*)-157** as a solid, m. p. 117-118 °C (EtOAc/hexane), ν_{max} (N) 2904, 2728, 2672, 1710 (overlapping C=O absorptions), 1580, 1461, 1377, 1312, 1298, 1237, 1196, 1120, 1085, 968, 860, 821, 797, 722, 707 and 685 cm^{-1}, δ_H 4.06 (3H, s, CO_2CH_3), 6.65 (1H, dd, *J* 16.0 and 7.5, *H*-2), 7.58 (1H, dd, *J* 8.0 and 4.5, *H*-5'), 8.04 (1H, dd, *J* 8.0 and 1.5, *H*-4'), 8.38 (1H, d, *J* 16.0, *H*-3), 8.78 (1H, dd, *J* 4.5 and 1.5, *H*-6') and 9.81 (1H, d, *J* 7.5, *H*-1) ppm, δ_C (100.6 MHz) 52.82 (CO_2CH_3), 126.29 (*C*-5'), 131.51 (*C*-3'), 132.07 (*C*-2), 135.50 (*C*-4'), 145.86 (*C*-2'), 147.59 (*C*-6'), 150.21 (*C*-3), 165.26 (CO_2CH_3) and 192.87 (*C*-1) ppm. HRMS : *m/z* 192.0663. *Calculated* for $[C_{10}H_9NO_3+H]^+$: 192.0661.

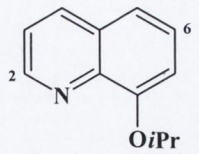


(*Z*)-157

(*Z*)-*3-(2'-carbomethoxypyrid-3'-yl)prop-2-enal* **(*Z*)-157** could never be separated by column chromatography but was clearly present in the crude ozonolysis mixture and had δ_H 3.96 (3H, s, CO_2CH_3), 6.26 (1H, dd, *J* 11.8 and 8.0, *H*-2), 7.52 (1H, dd, *J* 7.8 and 4.7, *H*-5'), 7.72 (1H, d, *J* 7.5, *H*-4'), 8.08 (1H, d, *J* 11.5, *H*-3), 8.75 (1H, d, *J* 4.5, *H*-6') and 9.62 (1H, d, *J* 8.5, *H*-1) ppm.

8-Isopropoxyquinoline 127

8-Hydroxyquinoline **95** (14.00 g; 96.4 mmol) and anhydrous potassium carbonate (34.60 g; 250 mmol) in DMF (150 mL) were stirred under N_2 at 80 °C for 75 min after which time 2-bromopropane (23.5 mL; 250 mmol) was slowly added in two portions. The mixture was stirred at 80 °C for another 3 h and then the cooled contents of the flask were diluted with water (500 mL) and extracted with dichloromethane. The combined organic extracts were washed with aqueous potassium hydroxide solution (5 %; 200 mL) in portions and then with water until the washings were no longer alkaline.

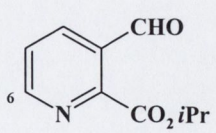


127

The dried and filtered extract was evaporated, leaving 8-isopropoxyquinoline **127** (13.00 g; 85 %) as an oil (*lit.*[97b] m. p. 41-43 °C), ν_{max} (L) 3458, 3162, 3082, 3026, 3010, 2960, 2852, 1736, 1723, 1574, 1451, 1432, 1304, 1286, 1262, 1225, 1196, 1139, 1081, 1057, 958, 845, 782, 763 and 731 cm^{-1}, δ_H 1.55 (6H, d, *J* 6.0, $OCH(CH_3)_2$), 4.87 (1H, septet, *J* 6.0, $OCH(CH_3)_2$), 7.09 (1H, d, *J* 7.5, *H*-7), 7.35-7.50 (3H, m, *H*-3, *H*-5 and *H*-6), 8.13 (1H, dd, *J* 8.0 and 1.5, *H*-4) and 8.98 (1H, dd, *J* 4.0 and 1.5, *H*-2) ppm.

Ozonolysis of 8-isopropoxyquinoline 127: isopropyl 3-formylpyridine-2-carboxylate 162

A three-necked flask (250 mL) fitted with a stirring bar and dropping funnel was placed in an ice-bath and connected to the ozoniser. 8-Isopropoxyquinoline **127** (13.00 g; 69.4 mmol), dissolved in methanol (150 mL), was added and the solution was subjected to a stream of ozonised O_2 (containing ~1.5 % O_3) for 4.5 h (O_2 flow rate of 2 L/min). Ozone production was discontinued and the system was flushed with O_2 for 20 min to purge excess reagent. Dimethyl sulfide (13 mL; 177.3 mmol) was slowly added *via* the dropping funnel while the mixture was continuously cooled in an ice-bath. After a further 30 min solvents were removed under reduced pressure.

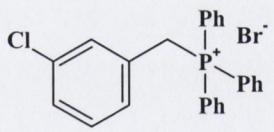


162

The viscous brown oil so obtained was taken up in ethyl acetate (100 mL) and the extract was washed with brine and dried. The crude oily product (13.40 g; 99 %) was used without further purification for olefination reactions, but an analytical sample of the aldehyde **162** was obtained by column chromatography (EtOAc/hexane) as an oil (*lit.*[98] an oil) that had ν_{max} (N) 3068, 2985, 2935, 2879, 1736, 1711, 1579, 1468, 1456, 1439, 1387, 1375, 1344, 1304, 1265, 1240, 1186, 1146, 1103, 1088, 916, 881, 868, 841, 822, 802, 762 and 714 cm^{-1}, δ_H 1.46 (6H, d, *J* 6.0, $OCH(CH_3)_2$), 5.40 (1H, septet, *J* 6.3, $OCH(CH_3)_2$), 7.60 (1H, dd, *J* 7.8 and 4.8, *H*-5), 8.26 (1H, dd, *J* 7.8 and 1.8, *H*-4), 8.89 (1H, dd, *J* 4.5 and 1.5, *H*-6) and 10.58 (1H, s, C*H*O) ppm.

3-Chlorobenzyltriphenylphosphonium bromide 159[93]

Triphenylphosphine (5.25 g; 20 mmol) was dissolved in toluene (75 mL) and to this was added 3-chlorobenzyl bromide (2.6 mL; 20 mmol). The mixture was heated under reflux for 4 h and was then allowed to cool down to room temperature. The precipitate that had formed was separated by suction filtration.

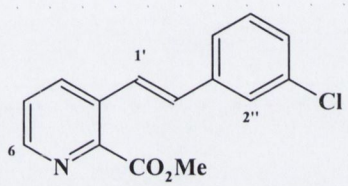


159

From this, *3-chlorobenzyltriphenylphosphonium bromide* **159** was obtained as white crystals (8.87 g; 95 %) that had ν_{max} (N) 2926, 2855, 2781, 1588, 1466, 1437, 1377, 1159, 1110, 996, 879, 813, 725 and 686 cm^{-1}, δ_H 5.58 (2H, d, $^2J_{H\text{-}P}$ 15.1, CH_2P), 6.87 (1H, d, *J* 2.0, *H*-2), 7.09 (1H, apparent t, *J* 7.8, *H*-5), 7.19 (1H, d, *J* 7.5, *H*-4), 7.28 (1H, d, *J* 7.5, *H*-6), 7.60-7.70 (6H, m, Ph-*H*'s) and 7.70-7.90 (9H, m, Ph-*H*'s) ppm.

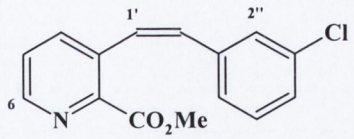
Wittig olefination of aldehyde 106: methyl (*E*)- and (*Z*)-3-(2'-(3"-chloro-phenyl)ethenyl)pyridine-2-carboxylate 107

3-Chlorobenzyltriphenylphosphonium bromide **159** (2.40 g; 5.1 mmol) was dissolved under N_2 in freshly distilled anhydrous THF (50 mL) at 0 °C and treated with *n*-butyllithium (2.5M in hexane: 2 mL; 5 mmol). After 30 min the temperature was decreased to –78 °C and the aldehyde **106** (0.80 g; 4.8 mmol), dissolved in THF (10 mL), was added. After 1 h the mixture was warmed to room temperature and stirring was continued overnight. It was then diluted with water (100 mL) and extracted with chloroform. The extract was dried, filtered and evaporated to give a mixture of the (*E*)- and (*Z*)-isomers of the stilbazole **107**, which were separated by column chromatography (EtOAc/hexane).



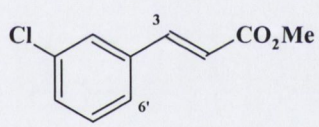
(*E*)-107

Methyl (E)-3-(2'-(3"-chlorophenyl)ethenyl)pyridine-2-carboxylate **(*E*)-107** had m. p. 73-74 °C (EtOAc/hexane), ν_{max} (N) 2953, 2922, 2852, 1730 (C=O), 1589, 1456, 1377, 1306, 1281, 1238, 1194, 1140, 1099, 1078, 991, 976, 966, 910, 889, 866, 858, 822, 810, 802, 777, 723, 712, 683 and 675 cm^{-1}, δ_H 3.95 (3H, s, CO_2CH_3), 6.86 (1H, d, *J* 16.0, *H*-2'), 7.14-7.23 (2H, m, *H*-4" and *H*-5"), 7.32 (1H, dt, *J* 7.0 and 1.5 and 1.5, *H*-6"), 7.37 (1H, dd, *J* 8.0 and 4.5, *H*-5), 7.42 (1H, d, *J* 2.0, *H*-2"), 7.82 (1H, d, *J* 16.6, *H*-1'), 7.94 (1H, dd, *J* 8.0 and 1.5, *H*-4) and 8.53 (1H, d, *J* 3.5, *H*-6) ppm, δ_C (100.6 MHz) 52.42 (CO_2CH_3), 124.65 (*C*-6"), 125.31 (*C*-1'), 125.89, 126.31 (*C*-5 and *C*-2"), 127.78 (*C*-4"), 129.46 (*C*-5"), 131.33 (*C*-2'), 133.96, 134.15 (*C*-3 and *C*-3"), 134.37 (*C*-4), 138.01 (*C*-1"), 145.01 (*C*-2), 147.71 (*C*-6) and 165.74 (CO_2CH_3) ppm. HRMS : *m/z* 274.0634. *Calculated* for $[C_{15}H_{12}ClNO_2+H]^+$: 274.0635.



(*Z*)-107

Methyl (Z)-3-(2'-(3"-chlorophenyl)ethenyl)pyridine-2-carboxylate **(*Z*)-107** had m. p. 50-51 °C (EtOAc/hexane), ν_{max} (N) 3384, 3188, 2954, 2924, 2854, 1718 (C=O), 1707, 1593, 1560, 1456, 1412, 1377, 1302, 1282, 1242, 1200, 1142, 1088, 958, 920, 899, 877, 833, 818, 793, 750, 704, 687 and 661 cm^{-1}, δ_H 3.90 (3H, s, CO_2CH_3), 6.61 (1H, d, *J* 12.0, *H*-2'), 6.81 (1H, d, *J* 7.5, *H*-4"), 6.95-7.01 (3H, m, *H*-1', *H*-2" and *H*-5"), 7.04 (1H, d, *J* 8.0, *H*-6"), 7.17 (1H, dd, *J* 7.8 and 4.7, *H*-5), 7.43 (1H, dd, *J* 7.5 and 1.0, *H*-4) and 8.52 (1H, d, *J* 4.5, *H*-6) ppm, δ_C (100.6 MHz) 52.21 (CO_2CH_3), 125.30 (*C*-5), 126.75 (*C*-4"), 126.93 (*C*-6"), 128.07, 128.52, 129.01 (*C*-1', *C*-2" and *C*-5"), 129.61 (*C*-2'), 133.66, 134.21 (*C*-3 and *C*-3"), 137.31 (*C*-1"), 138.75 (*C*-4), 145.88 (*C*-2), 147.84 (*C*-6) and 165.41 (CO_2CH_3) ppm. HRMS : *m/z* 274.0646. *Calculated* for $[C_{15}H_{12}ClNO_2+H]^+$: 274.0635.

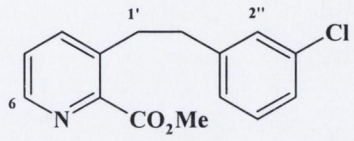


(*E*)-160

If the unpurified aldehyde **106**, obtained from the ozonolysis of 8-methoxyquinoline **105**, was used for the above Wittig reaction, methyl *(E)-3-(3'-chlorophenyl)prop-2-enoate* **160** could be isolated as an additional minor component during chromatography of the product mixture. Alkene **(*E*)-160**, a low-melting solid (*lit.*[95] m. p. 45-46.5 °C), had ν_{max} (N) 3063, 2952, 2925, 2852, 1722, 1641, 1595, 1568, 1467, 1435, 1376, 1317, 1201, 1174, 1106, 1979, 1038, 1015, 982, 884, 860, 788, 744 and 673 cm^{-1}, δ_H 3.83 (3H, s, CO_2CH_3), 6.46 (1H, d, *J* 16.0, *H*-2), 7.30-7.43 (3H, m, *H*-4', *H*-5' and *H*-6'), 7.52 (1H, s, *H*-2') and 7.64 (1H, d, *J* 16.0, *H*-3) ppm, δ_C (100.6 MHz) 51.41 (OCH_3), 118.80 (*C*-2), 125.80 (*C*-6'), 127.34 (*C*-2'), 129.69, 129.71 (*C*-4' and *C*-5'), 134.46 (*C*-3'), 135.72 (*C*-1'), 142.80 (*C*-3) and 166.57 (*C*-1) ppm.

Hydrogenation of methyl (*E*)- and (*Z*)-3-(2'-(3"-chlorophenyl)ethenyl)pyridine-2-carboxylates 107: methyl 3-(2'-(3"-chlorophenyl)ethanyl)pyridine-2-carboxylate 108

A mixture of (*E*)- and (*Z*)-isomers of the stilbazole **107** (0.40 g; 1.33 mmol) was dissolved in ethyl acetate (10 mL) and 5 % Pd/C catalyst (20 mg) was added. The mixture was hydrogenated at 1 atm until reaction was complete (~4 h).

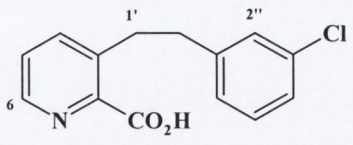


108

Catalyst was removed by filtration and solvent was evaporated to give the ester **108** as a solid that was recrystallised from ethyl acetate/hexane (0.36 g; 89 %), m. p. 54-55 °C (EtOAc/hexane), ν_{max} (N) 3066, 3053, 2953, 2922, 2852, 1726 (C=O), 1718, 1599, 1572, 1477, 1464, 1456, 1444, 1429, 1377, 1306, 1294, 1259, 1234, 1201, 1136, 1097, 1076, 968, 889, 868, 849, 820, 804, 769, 725, 702 and 683 cm^{-1}, δ_H 2.94 (2H, m, *H*-2'), 3.25 (2H, m, *H*-1'), 4.02 (3H, s, CO_2CH_3), 7.07 (1H, dd, *J* 6.5 and 2.0, *H*-6"), 7.18-7.26 (3H, m, *H*-2", *H*-4" and *H*-5"), 7.38 (1H, dd, *J* 7.8 and 4.8, *H*-5), 7.54 (1H, dd, *J* 8.0 and 1.5, *H*-4) and 8.61 (1H, dd, *J* 4.5 and 1.5, *H*-6) ppm, δ_C (100.6 MHz) 34.55 (*C*-1'), 36.61 (*C*-2'), 52.37 (CO_2CH_3), 125.68 (*C*-5), 125.93, 126.39, 128.24, 129.23 (*C*-2", *C*-4", *C*-5" and *C*-6"), 133.70 (*C*-3"), 138.18 (*C*-3), 139.12 (*C*-4), 142.58 (*C*-1"), 146.38 (*C*-2), 146.88 (*C*-6) and 165.79 (CO_2CH_3) ppm. HRMS : *m/z* 276.0798. *Calculated* for $[C_{15}H_{14}ClNO_2+H]^+$: 276.0791.

Hydrolysis of methyl 3-(2'-(3"-chlorophenyl)ethanyl)pyridine-2-carboxylate 108 to 3-(2'-(3"-chlorophenyl)ethanyl)pyridine-2-carboxylic acid 45

The methyl ester **108** (0.36 g; 1.31 mmol) was dissolved in ethanol (5 mL) with sodium hydroxide (0.20 g, 5 mmol) and water (20 mL) and the mixture was stirred for 48 h. It was then acidified using 1M HCl and extracted with chloroform.



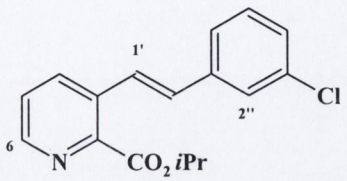
45

The organic layer was washed with brine, dried, filtered and evaporated to yield a colourless solid that was recrystallised from ethyl acetate to afford 0.30 g (88 %) of the acid **45**, m. p. 125-126 °C, ν_{max} (N) 3475, 3192, 3078, 2953, 2924, 2854, 1658, 1601, 1572, 1508, 1460, 1431, 1377, 1358, 1313, 1290, 1167, 1151, 1103, 1088, 1076, 1057, 1022, 995, 955, 891, 872, 849, 835, 800, 779, 692, 681 and 661 cm^{-1}, δ_H (DMSO-d_6) 2.87 (2H, m, *H*-2'), 3.10 (2H, m, *H*-1'), 7.18 (1H, d, *J* 7.5, *H*-6"), 7.26 (1H, d, *J* 7.8, *H*-4"), 7.28-7.35 (2H, m, *H*-2" and *H*-5"), 7.49 (1H, dd, *J* 7.8 and 4.8, *H*-5), 7.78 (1H, dd, *J* 7.5 and 1.0, *H*-4), 8.50 (1H, dd, *J* 4.8 and 1.2, *H*-6) and 13.16 (1H, s, CO_2H) ppm, δ_C (100.6 MHz) 33.74 (*C*-1'), 36.11 (*C*-2'), 125.78 (*C*-5), 126.02, 127.08, 128.21, 130.18 (*C*-2", *C*-4", *C*-5" and *C*-6"), 132.94 (*C*-3"), 136.30 (*C*-3), 139.10 (*C*-4), 143.77 (*C*-1"), 146.68 (*C*-6), 148.65 (*C*-2) and 167.58 (CO_2H) ppm. HRMS : *m/z* 262.0620. *Calculated* for $[C_{14}H_{12}ClNO_2+H]^+$: 262.0635.

Wittig olefination of aldehyde 162: isopropyl (*E*)- and (*Z*)-3-(2'-(3"-chloro-phenyl)ethenyl)pyridine-2-carboxylates 163

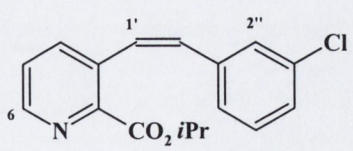
3-Chlorobenzyltriphenylphosphonium bromide **159** (14.00 g; 30 mmol) was dissolved under N_2 in freshly-distilled anhydrous THF (60 mL) at 0 °C. To this solution was added *n*-butyllithium (2.5M in hexane: 12 mL; 30 mmol) and stirring was continued for 30 min. The temperature was reduced to –70 °C and 3-formyl-2-carboisopropoxypyridine **162** (5.80 g; 30 mmol), in THF (10 mL), was added. After 30 min the mixture was warmed to room temperature and stirring was continued for a further 6 h. The mixture was diluted with water (200 mL), extracted using diethyl ether and the extract was dried, filtered and evaporated. Ether (50 mL) was added to the residue and the mixture was stirred and heated for 1 h and then filtered to remove insoluble triphenylphosphine oxide. The filtrate was evaporated and the oily residue was chromatographed (diethyl ether) to give a yellow oil (4.02 g; 44 %)

consisting mainly of the (*E*)- and (*Z*)-isomers of the stilbazole **163**. An analytical sample of the (*E*)-isomer could be obtained by further column chromatography (EtOAc/hexane) but the (*Z*)-isomer was always contaminated by traces of the (*E*)-form.



(*E*)-163

Isopropyl (E)-3-(2'-(3''-chlorophenyl)ethenyl)pyridine-2-carboxylate **(*E*)-163** was obtained as a solid that had m. p. 82-84 °C (EtOAc/hexane), ν_{max} (L) 2923, 2853, 2361, 2343, 1712, 1637, 1610, 1593, 1561, 1506, 1459, 1377, 1353, 1293, 1243, 1181, 1148, 1106, 1087, 1060, 956, 909, 870, 850, 806, 772, 737, 709 and 678 cm^{-1}, δ_H 1.49 (6H, d, *J* 6.2, $CH(CH_3)_2$), 5.40 (1H, septet, *J* 6.3, $CH(CH_3)_2$), 7.01 (1H, d, *J* 16.4, *H*-2'), 7.26-7.37 (2H, m, *H*-4'' and *H*-5''), 7.43 (1H, d, *J* 6.8, *H*-6''), 7.51 (1H, dd, *J* 8.0 and 4.5, *H*-5), 7.54 (1H, s, *H*-2''), 7.82 (1H, d, *J* 16.4, *H*-1'), 8.10 (1H, d, *J* 8.2, *H*-4) and 8.69 (1H, d, *J* 4.1, *H*-6) ppm, δ_C (100.6 MHz) 21.43 ($OCH(CH_3)_2$), 69.69 ($OCH(CH_3)_2$), 124.65 (*C*-6''), 125.22 (*C*-1'), 125.62 (*C*-5), 126.38 (*C*-2''), 127.96, 129.58 (*C*-4'' and *C*-5''), 131.50 (*C*-2'), 133.56 (*C*-3), 134.34 (*C*-3''), 134.89 (*C*-4), 138.01 (*C*-1''), 147.45 (*C*-2), 147.51 (*C*-6) and 164.8 (CO_2*i*-Pr) ppm. HRMS: *m/z* 302.0960. *Calculated* for $[C_{17}H_{16}ClNO_2+H]^+$: 302.0948.

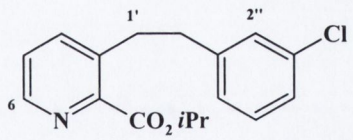


(*Z*)-163

Isopropyl (Z)-3-(2'-(3"-chlorophenyl)ethenyl)pyridine-2-carboxylate **(Z)-163** was obtained as an oil that had ν_{max} (N) 3059, 2962, 2920, 2848, 1716, 1630, 1592, 1560, 1466, 1373, 1298, 1261, 1184, 1144, 1105, 1084, 962, 918, 864, 827, 796, 752, 731, 710, 685 and 654 cm^{-1}, δ_H 1.41 (6H, d, *J* 5.8, $CH(CH_3)_2$), 5.31 (1H, septet, *J* 6.2, $CH(CH_3)_2$), 6.67 (1H, d, *J* 12.4, *H*-2'), 6.89 (1H, d, *J* 7.3, *H*-4"), 7.02 (1H, d, *J* 12.4, *H*-1'), 7.04-7.09 (2H, m, *H*-2" and *H*-5"), 7.12 (1H, dd, *J* 8.0 and 1.4, *H*-6"), 7.22 (1H, dd, *J* 7.7 and 4.8, *H*-5), 7.49 (1H, dd, *J* 8.0 and 1.5, *H*-4) and 8.61 (1H, dd, *J* 4.4 and 1.5, *H*-6) ppm, δ_C (100.6 MHz) 21.35 ($CH(CH_3)_2$), 69.29 ($CH(CH_3)_2$), 125.02 (*C*-5), 126.82 (*C*-4"), 126.98 (*C*-6"), 128.30, 128.59, 129.07 (*C*-1', *C*-2" and *C*-5"), 129.40 (*C*-2'), 133.71, 133.76 (*C*-3 and *C*-3"), 137.37 (*C*-1"), 138.65 (*C*-4), 146.99 (*C*-2), 148.04 (*C*-6) and 164.91 (CO_2i-Pr) ppm. HRMS: *m/z* 324.0763. *Calculated* for $[C_{17}H_{16}ClNO_2+Na]^+$: 324.0767.

Hydrogenation of isopropyl (*E*)- and (*Z*)-3-(2'-(3"-chlorophenyl)ethenyl)-pyridine-2-carboxylates 163: isopropyl 3-(2'-(3"-chlorophenyl)ethanyl)-pyridine-2-carboxylate 164

A mixture of the (*E*)- and (*Z*)-stilbazoles **163** (3.20 g; 10.6 mmol), in ethyl acetate (40 mL) with 5 **%** Pd/C catalyst (150 mg) was hydrogenated at 1 atm until uptake of hydrogen had ceased (*ca.* 48 h). Removal of catalyst and solvent yielded *isopropyl 3-(2'-(3"-chlorophenyl)ethanyl)pyridine-2-carboxylate* **164** (2.94 g; 91 %) as an oily solid that could not be satisfactorily recrystallised but that had m. p. 41-43 °C, ν_{max} (N) 3051, 2981, 2935, 2872, 1722 (C=O), 1599, 1572, 1479, 1450, 1439, 1387, 1375, 1354, 1336, 1298, 1232, 1194, 1182, 1146, 1107, 1095, 999, 918, 891, 866, 796, 783, 717, 702, 685 and 667 cm^{-1}, δ_H 1.46 (6H, d, *J* 6.0, $CH(CH_3)_2$), 2.94 (2H, m, *H*-2'), 3.19 (2H, m, *H*-1'), 5.36 (1H, septet, *J* 6.4, $CH(CH_3)_2$), 7.06 (1H, dt, *J* 6.6, 1.9 and 1.9, *H*-6"), 7.17-7.25 (3H, m, *H*-2", *H*-4" and *H*-5"), 7.34 (1H, dd, *J* 7.8 and 4.7, *H*-5), 7.50 (1H, dd, *J* 8.0 and 1.5, *H*-4) and 8.61 (1H, dd, *J* 4.8 and 1.2, *H*-6) ppm, δ_C (100.6 MHz) 21.37 ($CH(CH_3)_2$), 34.31 (*C*-1'), 36.53 (*C*-2'), 69.38 ($CH(CH_3)_2$), 125.28 (*C*-5), 125.97, 126.31, 128.19, 129.25 (*C*-2", *C*-4", *C*-5" and *C*-6"), 133.72 (*C*-3"), 137.28 (*C*-3), 139.29 (*C*-4), 142.48 (*C*-1"), 146.59 (*C*-6), 147.36 (*C*-2) and 164.97 (CO_2i-Pr) ppm. HRMS : *m/z* 304.1074. *Calculated* for $[C_{17}H_{18}ClNO_2+H]^+$: 304.1104.



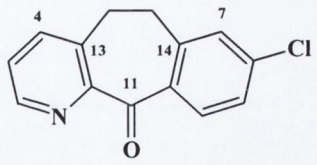
164

Hydrolysis of isopropyl 3-(2'-(3"-chlorophenyl)ethanyl)pyridine-2-carboxylate 164 to 3-(2'-(3"-chlorophenyl)ethanyl)pyridine-2-carboxylic acid 45

The isopropyl ester **164** (2.70 g; 8.89 mmol) was dissolved in ethanol (10 mL) with sodium hydroxide (0.70 g; 17.5 mmol) in water (50 mL) and the contents of the flask were refluxed for 5 h. After this time the solution was acidified using 1M HCl and extracted with chloroform. The extract was washed with brine, dried, filtered and evaporated to give a colourless solid that was recrystallised from ethyl acetate to afford the acid **45** (2.10 g; 90 %). The spectral data obtained for this compound is identical to that obtained for the product of the hydrolysis of the methyl ester **108**. This data is presented in this section on page 90.

Intramolecular cyclisation of the acid 45: 8-chloro-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridine-11-one 42

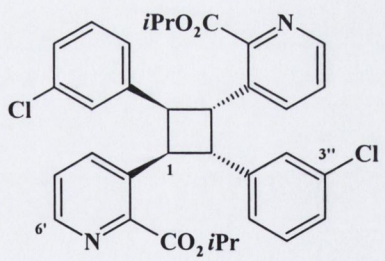
To the acid **45** (0.60 g; 23 mmol), dissolved in dichloromethane (30 mL), was added thionyl chloride (0.5 mL; 69 mmol) under a nitrogen atmosphere, and the mixture was stirred under reflux for 2 h. The solvent and excess reagent were evaporated off and the residue, a brown, viscous oil, was redissolved in DCM (30 mL). Anhydrous aluminium chloride (0.69 g; 69 mmol) was added and the contents of the flask were stirred overnight. The mixture was acidified with 2M HCl to pH 2, and the solution was extracted three times with diethyl ether (50 mL each). Then, the aqueous layer was basified with a 1M NaOH solution to pH 10, and this mixture was extracted with chloroform ($CHCl_3$). The chloroform extracts were dried and evaporation of the solvent afforded a crystalline solid, which was recrystallised from $CHCl_3$/hexane to yield the tricyclic ketone **42** (0.24 g; 43 %).



42

8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-one **42**, m. p. 106-107 °C ($CHCl_3$/hexane) (*lit.*[18] 100-101 °C, isopropyl ether), ν_{max} (N) 2927, 2855, 1664, 1644, 1584, 1555, 1453, 1408, 1377, 1356, 1330, 1294, 1229, 1212, 1191, 1166, 1150, 1087, 945, 907, 864, 838, 807, 794, 732 and 681 cm^{-1}, δ_H (DMSO-d_6) 3.11-3.18 (2H, m, *H*-5), 3.20-3.26 (2H, m, *H*-6), 7.47 (1H, dd, *J* 8.5 and 2.0, *H*-9), 7.51 (1H, s, *H*-7), 7.52 (1H, dd, *J* 8.0 and 5.0, *H*-3) 7.85 (1H, dd, *J* 8.0 and 2.0, *H*-4) 7.87 (1H, d, *J* 8.5, *H*-10) and 8.59 (1H, dd, *J* 4.8 and 1.7, *H*-2) ppm, δ_C (100.6 MHz) 30.83 (*C*-5), 33.57 (*C*-6), 126.32 (*C*-3), 126.85 (*C*-9), 130.02 (*C*-7), 131.92 (*C*-10), 135.58 (*C*-15), 136.47 (*C*-13), 137.44 (*C*-8), 137.46 (*C*-4), 144.15 (*C*-14), 148.10 (*C*-2), 154.45 (*C*-12) and 193.52 (*C*-11) ppm. HRMS: *m/z* 244.0546. *Calculated* for $[C_{14}H_{10}ClNO + H]^+$: 244.0529.

***cis,anti,cis*-Di-1,3-(3'-chlorophenyl)-2,4-di-(-2-carboisopropoxypyrid-3"-yl)-cyclobutane 166a**



166a

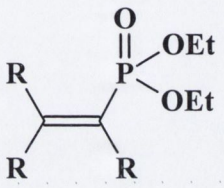
This compound (30 mg) was isolated during chromatographic purification of the stilbazoles **163** and had m. p. 40-42 °C (EtOAc/hexane), ν_{max} (N) 3408, 3064, 2954, 2926, 2872, 2852, 2229, 1718 (br, C=O), 1595, 1572, 1456, 1375, 1298, 1228, 1184, 1146, 1088, 1024, 999, 916, 862, 822, 789, 733, 694, 669 and 648 cm^{-1}, δ_H 1.40 (6H, d, *J* 6.0), 1.42 (6H, d, *J* 6.5) [$CH(CH_3)_2$ groups], 4.66 (2H, dd, *J* 10.0 and 8.0, *H*-1 and *H*-3), 5.15 (2H, dd, *J* 10.0 and 8.0, *H*-2 and *H*-4), 5.27 (2H, septet, *J* 6.3, $CO_2CH(CH_3)_2$ groups), 6.92-6.98 (2H, m, *H*-6'), 7.00-7.08 (4H, m, *H*-4' and *H*-5'), 7.12 (2H, s, *H*-2'), 7.39 (2H, dd, *J* 8.0 and 5.0, *H*-5"), 7.87 (2H, dd, *J* 8.0 and 1.0, *H*-4") and 8.52 (2H, dd, *J* 4.5 and 1.0, *H*-6") ppm, δ_C (100.6 MHz) 21.24, 21.31 ($CH(CH_3)_2$), 43.25 (*C*-2 and *C*-4), 45.41 (*C*-1 and *C*-3), 69.38 ($CH(CH_3)_2$), 125.43 (*C*-5"), 125.73 (*C*-6'), 126.48 (Ph-*C*H), 127.89 (*C*-2'), 129.09 (Ph-*C*H), 133.69 (*C*-3'), 135.85 (*C*-4"), 136.14 (*C*-3"), 140.67 (*C*-1'), 146.71 (*C*-6"), 146.98 (*C*-2") and 165.04 (CO_2i-Pr) ppm, C-H coupling constant: $^1J_{C\text{-}H}$ for *C*-1, *C*-2, *C*-3 and *C*-4 = 141 Hz. HRMS : *m/z* 603.1835. *Calculated for* $[C_{34}H_{32}Cl_2N_2O_4+H]^+$: 603.1817.

CHAPTER 3:

Synthesis of novel vinylphosphonates *via* Stobbe-like reactions

3.1 Introduction

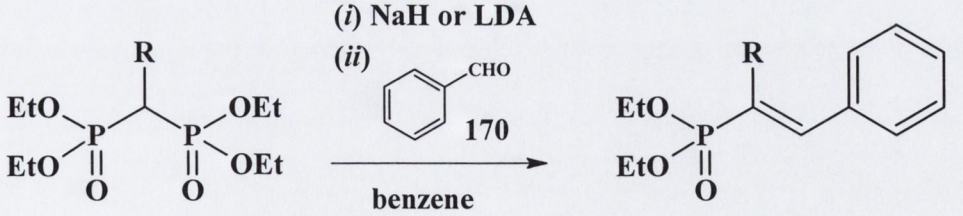
Vinylphosphonates have been known for a long time and have become valuable building blocks and precursors in organic synthesis.[103] Numerous syntheses of phosphonic acid esters have been reported,[103-113] but some of these lack stereoselectivity, give low yields or employ starting materials that are difficult to obtain. A few examples of both stereoselective and non-stereoselective vinylphosphonate preparations are described below.



Vinylphosphonates

3.1.1 Synthesis of vinylphosphonates *via* Horner-Emmons or Wittig reactions

One of the simplest reactions to obtain the title compounds is probably a standard Horner-Emmons olefination between tetraethyl methanediphosphonate **169a**, and an aldehyde or ketone.[104,105] As shown in **Scheme 3.1**, a benzene solution of the derivative **169a** is treated with base, sodium hydride or lithium diisopropylamide (LDA), and the carbanion of **169a** is reacted with an aldehyde or ketone, in this case benzaldehyde **170**, to give diethyl [(*E*)-2-phenylvinyl]phosphonate **171a**.



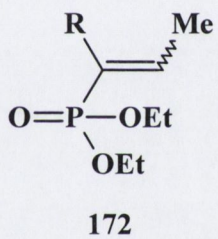
169 R = H or alkyl
169a R = H

171 R = H or alkyl
171a R = H

Scheme 3.1: Preparation of vinylphosphonates *via* Horner-Emmons reaction.

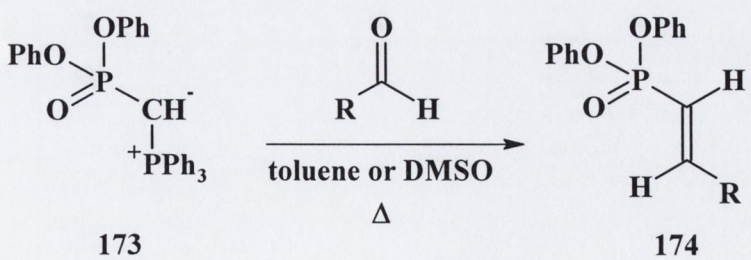
The geometry of the products **171** in **Scheme 3.1** is mostly influenced by the substituent R in the reagent **169**. Waszkuc *et al.*[104] employed only the bisphosphonate **169a** which, after deprotonation, was reacted with several aliphatic and aromatic aldehydes and ketones. All reactions carried out by these authors yielded solely products with an (*E*)-configured double bond. Aboujaoude, Lietjé and Collignon reported[105] on reactions of carbanions of **169** where R was represented by a lower alkyl or chlorine moiety. In this case the addition of aldehydes or unhindered ketones to deprotonated **169** afforded mixtures of (*E*)- and (*Z*)-isomers, the ratio of which was directly influenced by the size of R. **Table 3.1** shows how the (*E*)/(*Z*) ratio of the vinylphosphonate **172**, derived from acetaldehyde, can be manipulated by changing the size of the substituent R.

Table 3.1: Influence of the substituent R on the *cis-trans* ratio of vinylphosphonates **172**.

Entry	R	(*E*)/(*Z*) ratio of 174	
172a	H	100/0	
172b	Me	95/5	
172c	Et	57/43	
172d	Cl	89/11	

172

Similarly to the reaction shown in **Scheme 3.1**, β-substituted vinylphosphonates were also be prepared[106] from Wittig reactions of the ylid **173** (**Scheme 3.2**).



173 **174**

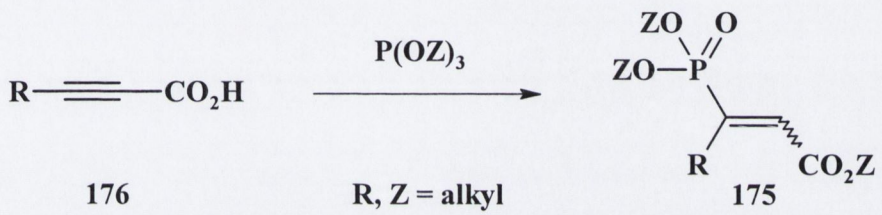
R = alkyl, aryl

Scheme 3.2: Synthesis of β-substituted vinylphosphonates **174** by Wittig reactions.

The Wittig-olefination shown in **Scheme 3.2** produced the unsaturated esters **174** in high yields, and from the NMR spectra of these compounds, more specifically from the observed ^{31}P-^{1}H coupling constants, it was deduced[106] that exclusively the (*E*)-isomers of **174** had been formed. The importance of ^{31}P-^{1}H coupling constants with regard to the assignment of the double bond geometry of vinylphosphonates will be discussed in **Section 3.6 (p129)**.

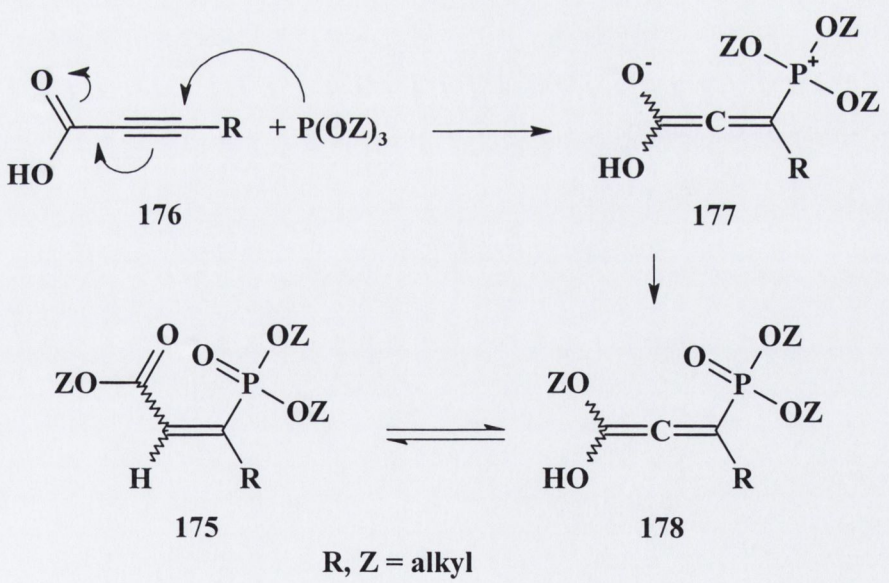
3.1.2 Synthesis of vinylphosphonates from acetylene derivatives

In 1963 Kirillova and coworkers[107] reported on the preparation of *β*-carboalkoxy-vinylphosphonates **175** which were synthesised from acetylenic acids **176** and trialkyl phosphites (**Scheme 3.3** and **Scheme 3.4**).



176 **R, Z = alkyl** **175**

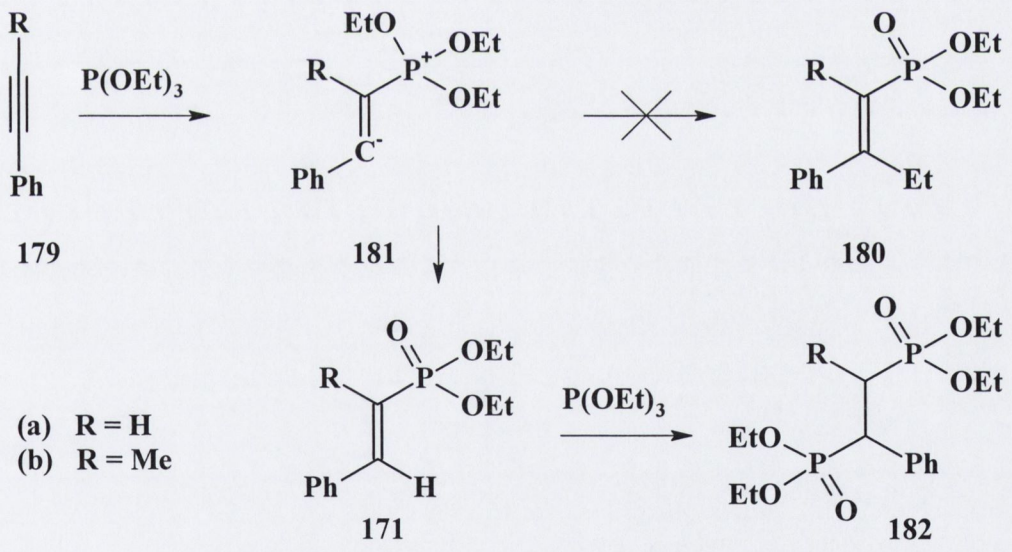
Scheme 3.3: Preparation of *β*-carboalkoxyvinylphosphonates **175** from acetylenic acids **176**.



Scheme 3.4: 1,4-Addition mechanism in the synthesis of *β*-carboalkoxy-vinylphosphonates **175**.

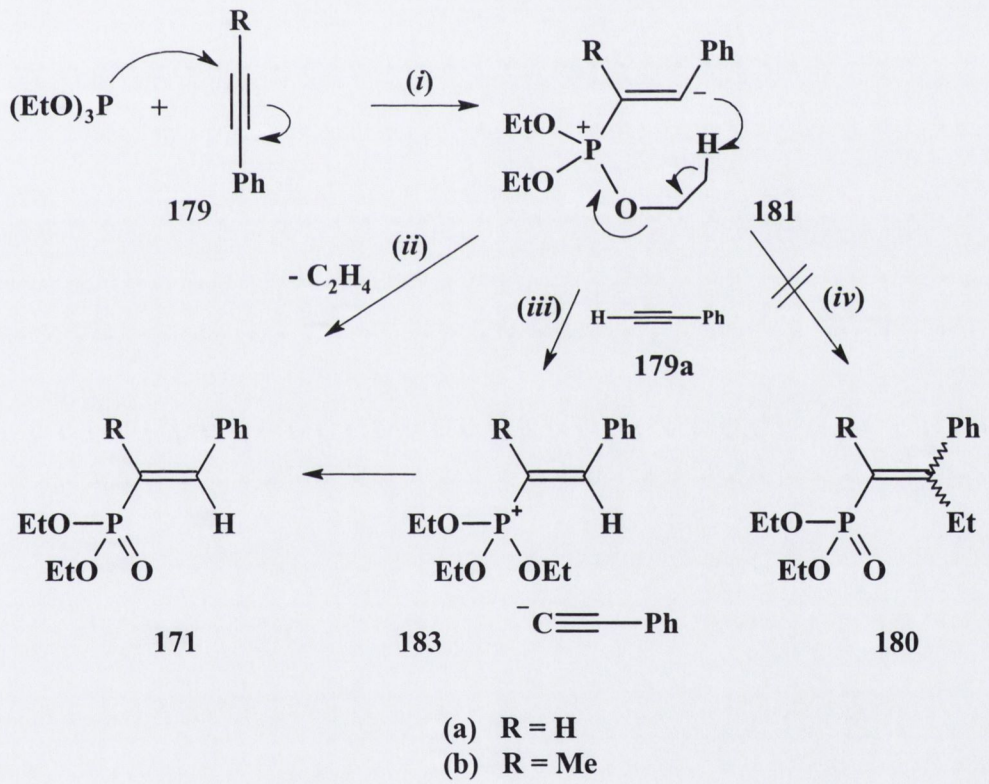
The authors postulated[107] that the reaction might proceed *via* an 1,4-addition mechanism (**Scheme 3.4**), which starts with nucleophilic attack of the phosphorus of the phosphite on *C*-3 of the acid **176** to give a zwitterion **177**. This betaine **177** then undergoes an internal oxygen to oxygen transalkylation to yield an enolic allene **178** which tautomerises to the ester **175**.

The striking ease and facility of the experiments depicted in **Scheme 3.3** and **3.4** tempted Griffin and Mitchell[108] to investigate addition reactions of trialkylphosphites to non-activated acetylenes. However, neither the reactions with the terminal acetylene **179a** nor reactions with the non-terminal alkyne **179b** afforded the desired β-sustituted vinylphosphonates **180** (**Scheme 3.5**). Besides large amounts of tars, only the *trans*-isomers of the vinyl esters **171**, which were believed to have been formed *via* the intermediates **181**, could be isolated as minor products. A large excess of phosphite reagent increased the yields of **171** slightly, but also led to the formation of α,β-bis(alkylphosphono)alkanes **182**. In a different experiment the latter compounds were also prepared directly from **171** and triethyl phosphite.



Scheme 3.5: Attempted synthesis of the β-substituted vinylphosphonates **180** from acetylenes **179**.

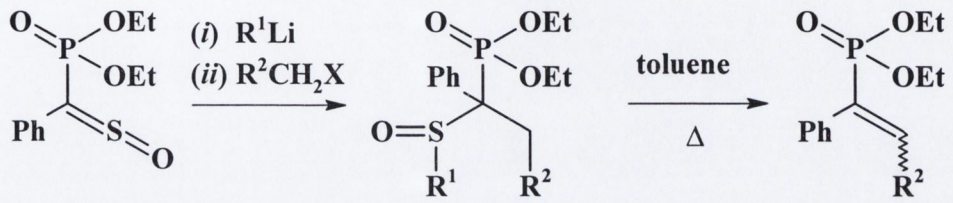
To explain the unanticipated formation of the unsaturated esters **171** the authors[108] proposed a mechanism which is depicted in **Scheme 3.6**. For non-terminal acetylenes, the mechanism is believed to proceed *via* a nucleophilic addition (*i*) of triethyl phosphite to, *e.g.*, methylphenylacetylene **179b** to give the intermediate **181b**. This step is followed by a *cis*-*β*-elimination (*ii*) to yield the (*E*)-vinylphosphonate **171b** and ethene. In cases where terminal acetylenes were used, for example phenylacetylene **179a**, another mechanism (*iii*) has been proposed. Here, protonation of the zwitterion **181a** by a second molecule of **179a** gives the phosphonium salt **183**, and subsequent dealkylation of the phosphonate group of **183** yields the vinylic ester **171a**. As has been mentioned above, formation of the expected product **180** from an alkyl transfer from oxygen to carbon according to route (*iv*) was not observed.[108]



Scheme 3.6: Various mechanistic pathways for the reaction between triethyl phosphite and the phenylacetylenes **179**.

3.1.3 Synthesis of vinylphosphonates from phosphoryl-substituted sulfines

Research into the area of phosphoryl-substituted sulfines by Zwanenburg, Porskamp and Lammerink led to a new synthetic route towards vinylphosphonates.[109] Thiophilic addition of alkyllithium to the sulfine **184** and subsequent alkylation gave the sulfinyl phosphonates **185**. The vinylphosphonates **186** were obtained upon heating of **185** in refluxing toluene (**Scheme 3.7**).



184 **185** **186**

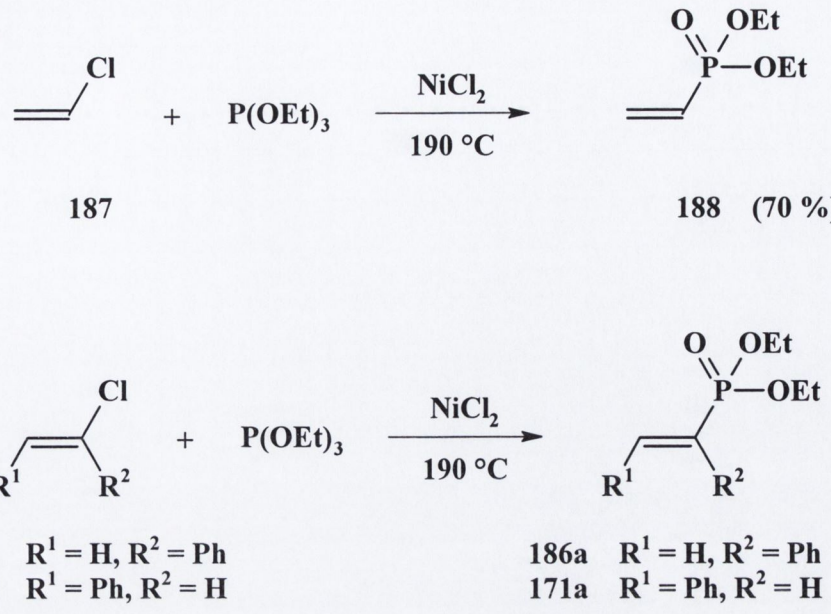
R^1 = Me or *n*-Bu R^2 = H or Ph X = I or Br

Scheme 3.7: Preparation of the vinylphosphonates **186** from the sulfines **184**.

However, the number of steps and the overall yield are not in favour of this route, thus, it might only be used for the synthesis of some not easily accessible derivatives **186**.

3.1.4 Transition metal-catalysed synthesis of vinylphosphonates

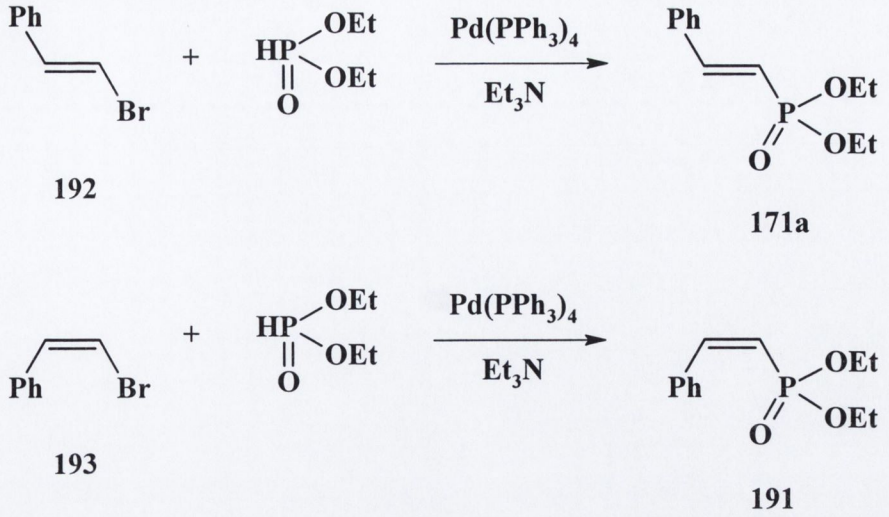
Syntheses of vinylphosphonates employing metals or metal complexes have been investigated extensively in the last couple of decades.[110-113] Tavs and Weitkamp[110] reported on successful reactions between trialkyl phosphites and vinyl halides. For example, when triethyl phosphite solutions of nickel chloride or nickel bromide were added to ethylene chloride **187** in an autoclave at high temperatures (~190 °C), this reaction yielded 70 % of diethyl vinylphosphonate **188** after distillation of the product mixture (**Scheme 3.8**). Under the same conditions, the nickel-catalysed reactions between triethyl phosphite and α- and *trans*-β-chlorostyrene **189** and **190**, respectively, afforded the expected phosphonic esters **186a** and **173a** in 46 and 52 % of the theoretical yields, respectively (**Scheme 3.8**).[110]



Scheme 3.8: Nickel chloride-catalysed synthesis of vinylphosphonates.

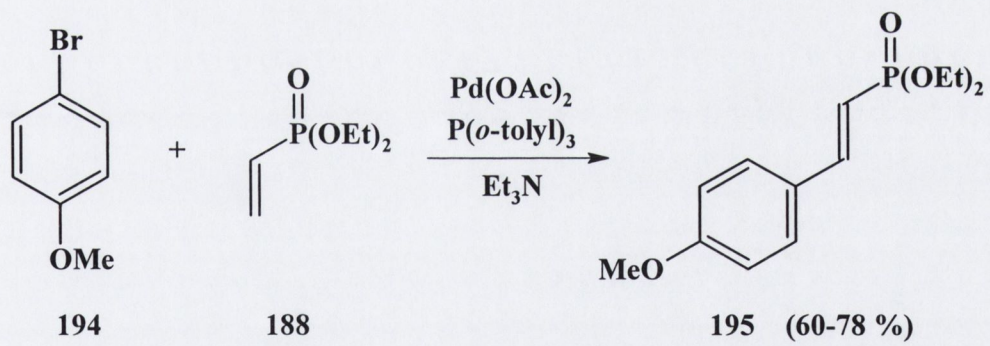
From the coupling constants J_{HH} and J_{PH} of the vinylic protons of the product 171**a** it was deduced that the phenyl group and the phosphonate group must have a *trans*-relationship.[110]

In an extension of their previous work, Hirao *et al.*[111] investigated the palladium-catalysed reactions of a variety of vinyl bromides (**Scheme 3.9**). The latter compounds were added to mixtures of triethylamine, a dialkyl phosphite and catalytic amounts of tetrakis(triphenylphosphine)palladium at 90 °C, and from these mixtures the authors[111] obtained dialkyl vinylphosphonates in usually excellent yields. Besides the high efficiency of these reactions, the products also retained the original double bond geometry of the starting materials. The synthesis of *trans*- and *cis*-phenylvinyl phosphonate 171**a** and **191**, respectively, derived from *trans*- and *cis*-bromostyrene **192** and **193**, respectively, may serve as an example for a number of experiments conducted by the above-mentioned researchers (**Scheme 3.9**).



Scheme 3.9: Stereoselective palladium-catalysed syntheses of (*E*)- and (*Z*)-styrylphosphonates **171a** and **191**.

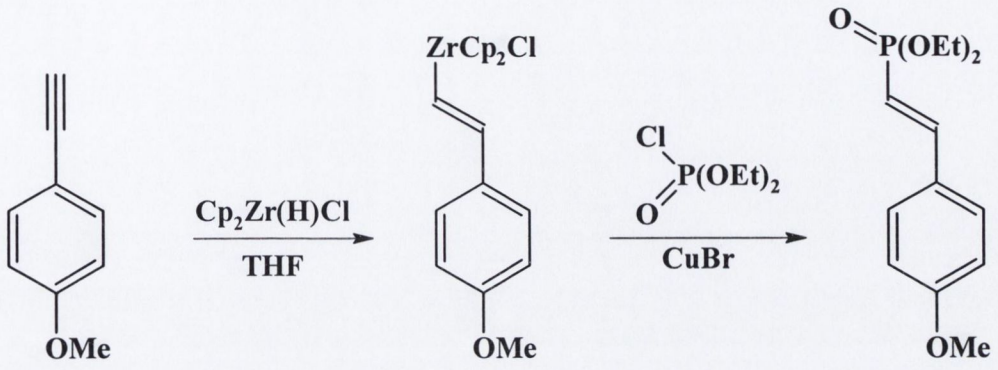
An alternative preparation of 2-arylvinylphosphonates has been reported by Xu, Huang and Huang.[112] In this case, aryl bromides like 4-methoxybromobenzene **194** underwent Heck reactions with diethyl ethenylphosphonate **188** in the presence of palladium acetate, tri-*ortho*-tolylphosphine and triethylamine (**Scheme 3.10**). The desired aryl-substituted vinylphosphonates, *e.g.* **195**, were obtained in yields between 60 and 78 %, and were exclusively present in their (*E*)-forms.



Scheme 3.10: Palladium-catalysed arylation of ethenylphosphonate **188**.

More recently, Zhong, Huang and Xiong have published[113] a stereoselective route towards (*E*)-2-arylvinylphosponates, the synthesis of which was achieved by means of vinylzirconium complexes. The latter were prepared by simply mixing terminal alkynes, for example 4-methoxyphenylacetylene **196**, with chlorobis(η^5-2,4-cyclo-

pentadien-1-yl)hydrozirconium ($Cp_2Zr(H)Cl$) in tetrahydrofuran (THF) for 20 minutes at room temperature. To the thus obtained metal complex **197**, the addition of diethyl chlorophosphate in the presence of copper(I) bromide gave exclusively the desired (*E*)-2-arylvinylphosponate **195** (**Scheme 3.11**).

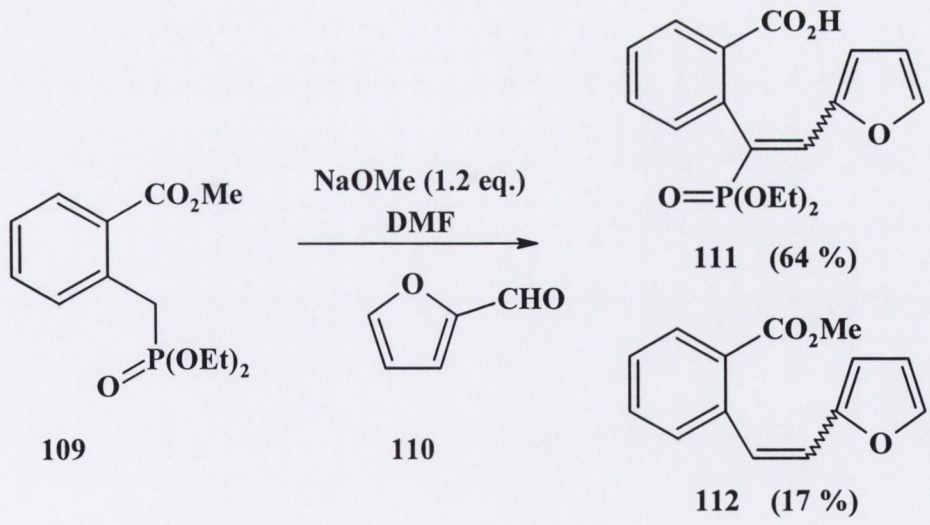


196 **197** **195**

Scheme 3.11: Synthesis of the (*E*)-2-arylvinylphosphonate **195**.

3.1.5 Vinylphosphonate synthesis by means of Stobbe-like reactions

In connection with the project discussed in **Chapter 2**, the following reaction, which has also been shown in **Section 1.8 (p41)**, was of special interest.

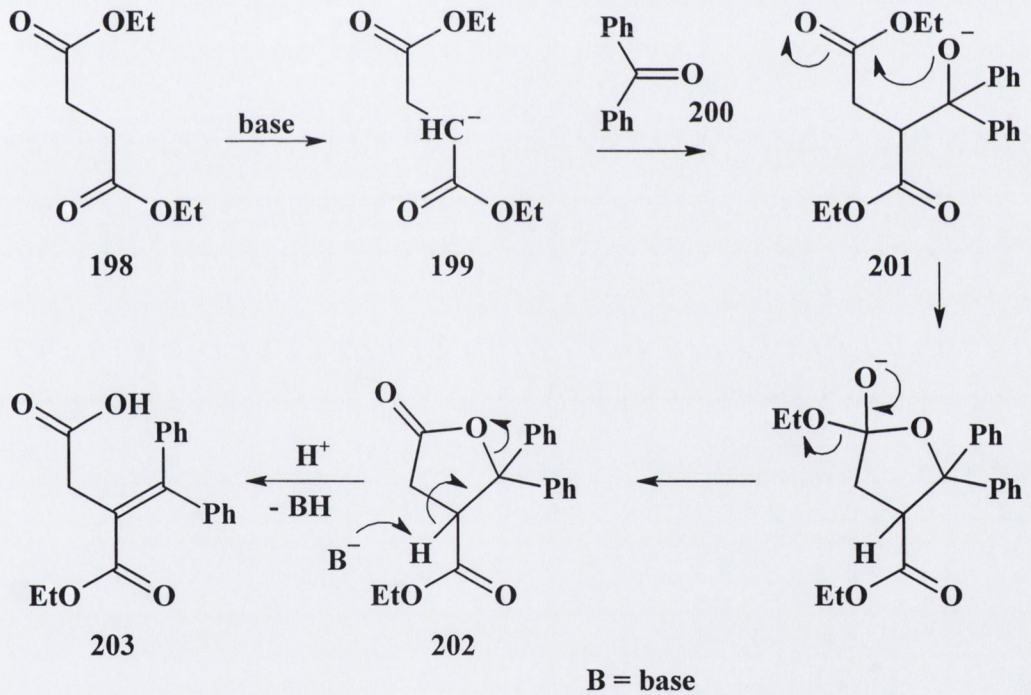


109 **110** **111 (64 %)** **112 (17 %)**

Scheme 3.12: Horner-Emmons and Stobbe-like reaction of the anion of phosphonate **109**.

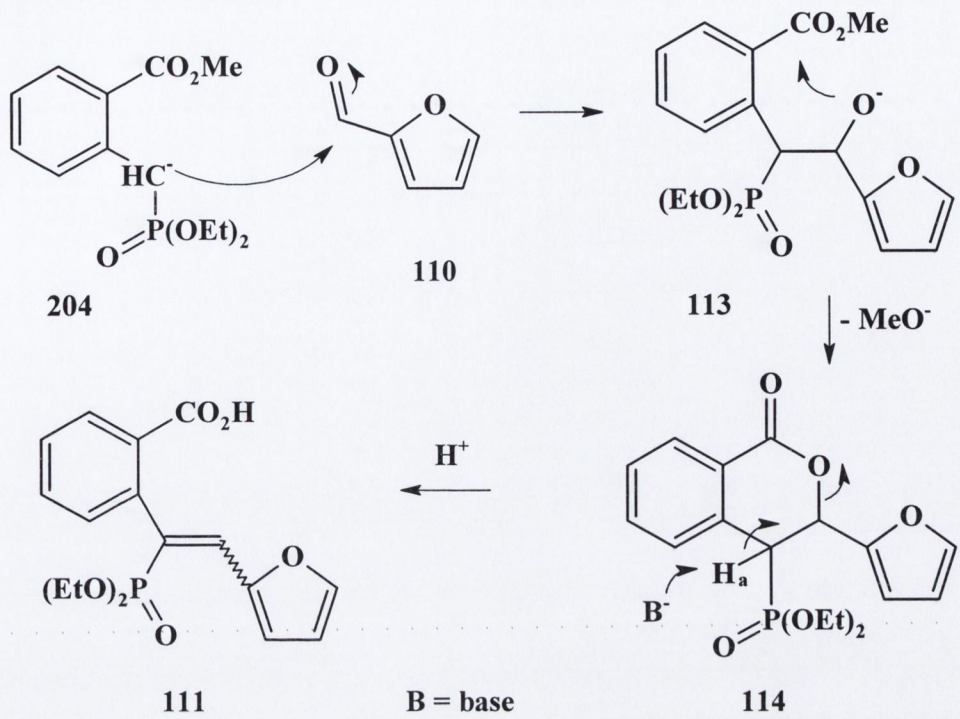
When O'Neill[60] attempted the reaction of deprotonated diethyl (2-carbomethoxy)-benzylphosphonate **109** with 2-furaldehyde **110** in DMF, the organic extracts of the reaction mixture contained only very small amounts (17 %) of the desired unsaturated ester **112**. The acidified aqueous washings contained the major product, which was identified as the novel vinylphosphonate **111** (no yield given) (**Scheme 3.12**).

The unexpected formation of the vinylphosphonate **111** was thought to proceed *via* a Stobbe-like mechanism. In the classical Stobbe-reaction,[59] for example, diethyl succinate **198** is deprotonated with an appropriate base, *e.g.*, sodium hydride, and the resulting carbanion **199** adds to an aldehyde or ketone, such as benzophenone **200**. The oxy-anion **201** undergoes cyclisation to yield the lactone intermediate **202**, which is finally converted into the vinylic compound **203** by deprotonation and collapse of the lactone ring *via* β-elimination of carboxylate ion (**Scheme 3.13**).



Scheme 3.13: Stobbe-mechanism for the reaction between diethyl succinate anion **199** and benzophenone **200**.

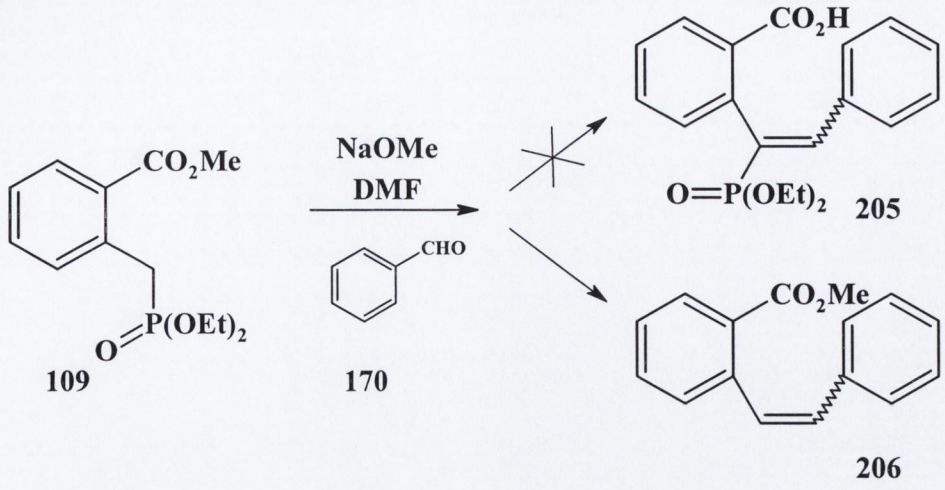
In his work O'Neill[60] used the mechanism shown above to explain the formation of the unexpected product **111** in the following way (**Scheme 3.14**):



Scheme 3.14: Mechanism of the reaction that leads to the vinylphosphonate **111**.

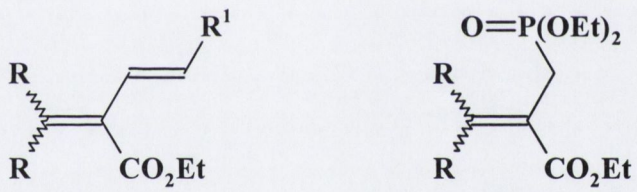
Nucleophilic attack of the carbanion **204** at the carbonyl group of the aldehyde **110** leads to the oxy-anion **113**. The negatively charged oxygen of **113** then forms a bond with the carboxyl ester group carbon and after the elimination of methoxide ion this process yields the six-membered lactone **114**. Abstraction of the α-proton H_a of the phosphonate **114** by a molecule of base induces β-elimination of carboxylate ion, and the acidification of this mixture during work-up then affords the free acid **111**.

Very similar to the experiment shown in **Scheme 3.12**, O'Neill[60] also attempted the reaction between the deprotonated phosphonate **109** and benzaldehyde **2**, using the same reaction conditions and work-up procedures. On this occasion, however, no vinylphosphonate **43** was reported to have formed, the Horner-Emmons product **44** being obtained as the sole product (**Scheme 3.15**). An explanation for this was not apparent, but it was suggested that "the electron-donating heterocyclic oxygen of 2-furaldehyde **31** profoundly influences the course of the reaction."[60]



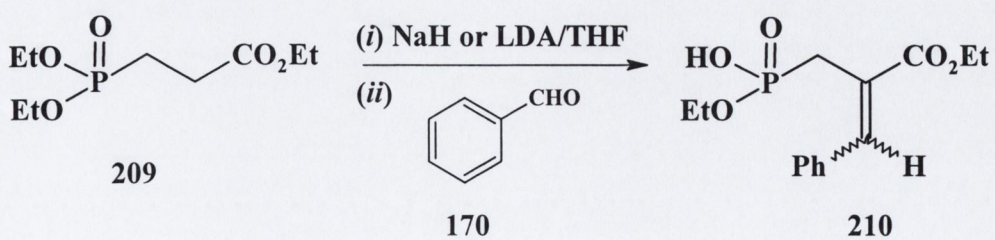
Scheme 3.15: Stobbe-like reaction which reportedly yields only the "normal" Horner-Emmons product **206** and not the vinylphosphonate **205**.

A literature search revealed that indeed Stobbe-like condensations have been used before to prepare vinylphosphonates. In an attempt to synthesise substituted ethyl 1,3-butadiene-2-carboxylates **207**, Bodalski and Janecki[114] employed Stobbe-like reactions to obtain the diethyl α-carboethoxyvinylphosphonate precursors **208**.



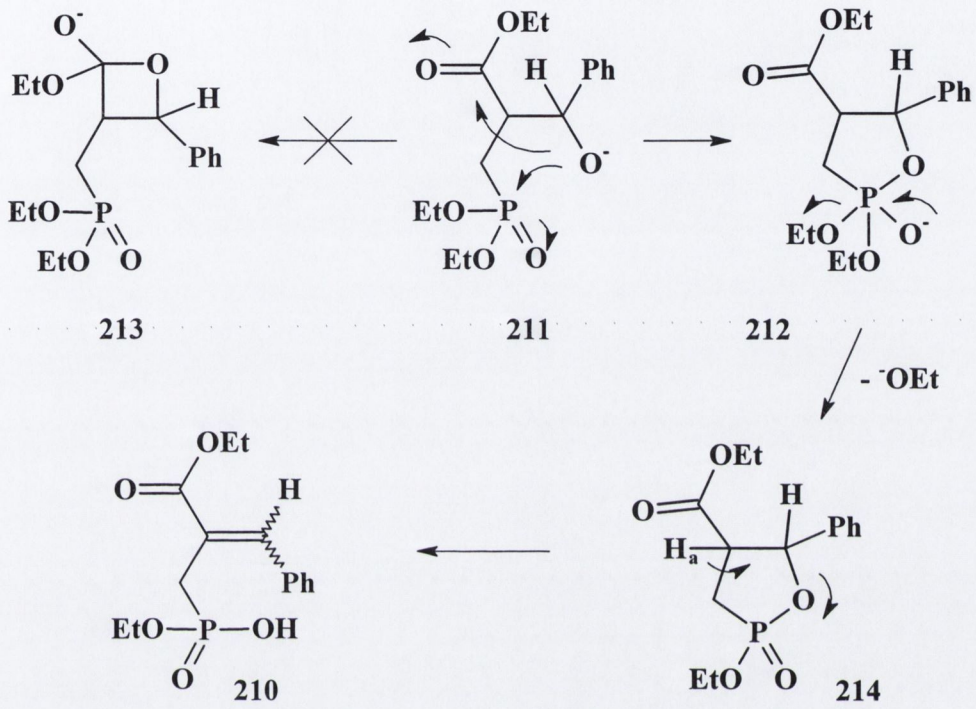
R = H, alkyl, aryl; R^1 = *i*-Pr or Ph

The synthesis started with the deprotonation of ethyl 3-(diethylphosphono)-propionate **209** with sodium hydride or LDA, and the subsequent addition of an aldehyde or ketone, in the present example benzaldehyde **170**, led to the phosphonic monoester **210** (**Scheme 3.16**).



Scheme 3.16: Stobbe-like reactions to prepare vinylcarboxylates like **210**.

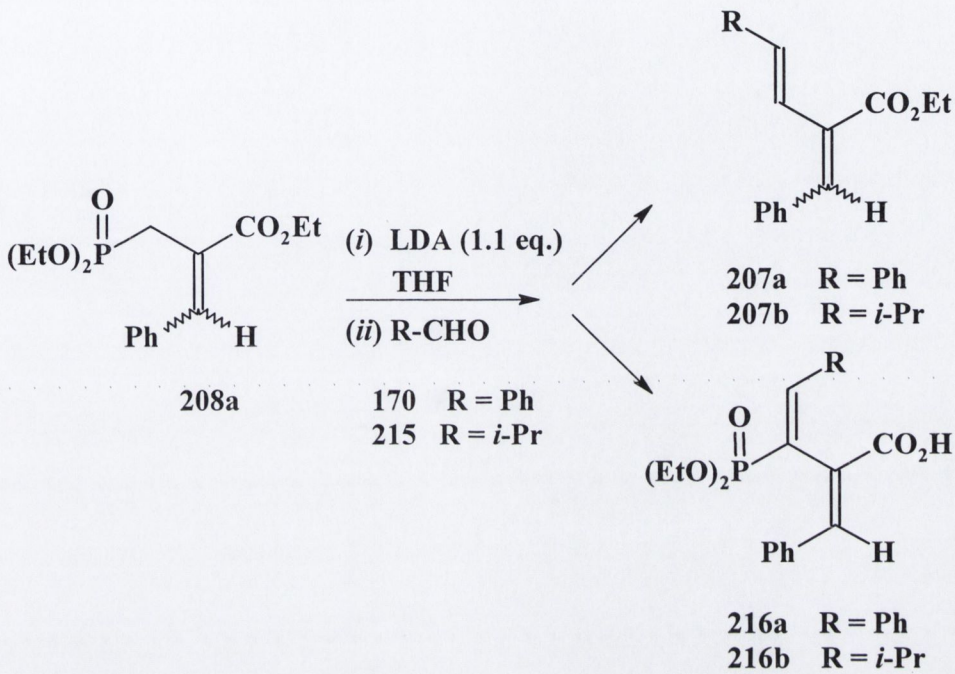
The oxy-anion **211**, formed during the reaction shown in **Scheme 3.16**, underwent cyclisation to give a five-membered ring (intermediate **212**), which is prefered to the formation of the more strained four-membered intermediate **213**. The diethyl-phosphono ester **212** eliminated ethoxide ion to yield the cyclic phosphononate **214**. The ring-opening of the intermediate **214** was triggered by the abstraction of the proton H_a and from this compound **210** was obtained (**Scheme 3.17**).



Scheme 3.17: Stobbe-like mechanism towards the P-monoethyl phosphonate **210**.

The phosphonic P-monoesters, including compound **210**, were next converted into the full esters **208** by means of thionyl chloride and ethanol. The thus obtained vinylcarboxylates **208** were then employed in Horner-Emmons olefinations (**Scheme 3.18**), which were used to prepare the aforementioned ethyl 1,3-butadiene-2-carboxylates **207**. The reaction afforded the desired products **207** in good yields. However, when the phosphonate **208a**, which was present as a (10:90)-mixture of its (E)- and (Z)-isomers, was reacted with benzaldehyde **170** or with isobutyraldehyde **215**, a mixture of compounds was obtained. Besides the expected alkadiene-carboxylates **207a** and **207b**, respectively, the vinylphosphonates **216a** and **216b** had also formed (**Scheme 3.18**).

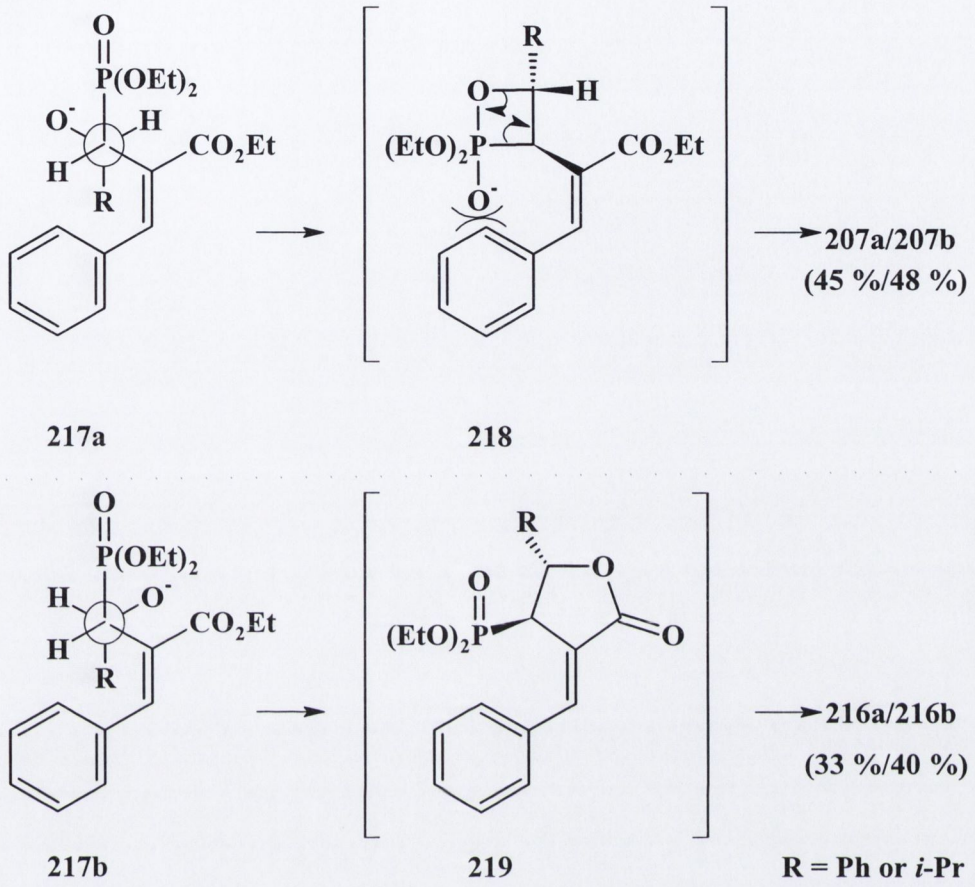
The authors reported[114] that the newly formed double bond of each of the dialkenes **207a** and **207b** had exclusively an (*E*)-configuration. The other vinyl group of **207a** and **207b** was also mostly present in its (*E*)-form (>95 %). The two double bonds of each of the phosphonic acid esters **216a** and **216b**, however, had a *cis-trans* relationship.



Scheme 3.18: Horner-Emmons reactions yielding mixtures of the alkadiene-carboxylates **207a** and **207b** and the vinylphosphonates **216a** and **216b**.

The occurrence of the vinylphosphonates **216a** and **216b** was ascribed[114] to the geometry of the starting material **208a** and to the stereochemistry of the initially formed oxy-anions **217a** and **217b** (**Scheme 3.19**). The (*Z*)-bonded phenyl group sterically hinders the stabilisation of the oxaphosphetane **218**, which is formed *via* **217a** and which leads to the Horner-Emmons products **207a** and **207b**. In a second unexpected Stobbe-like reaction of this synthetic route, the negatively-charged oxygen of the isomer **217b** attacks the carbonyl function to yield the five-membered lactone **219**. The latter is readily hydrolysed during the acidic work-up to give the vinylphosphonates **216a** and **216b**, respectively (**Scheme 3.19**).

As will be shown later in this Chapter, another factor, *i.e.*, the amount of base used in those reactions, might have also played an important part in the formation of the Stobbe-products **216a** and **216b**.

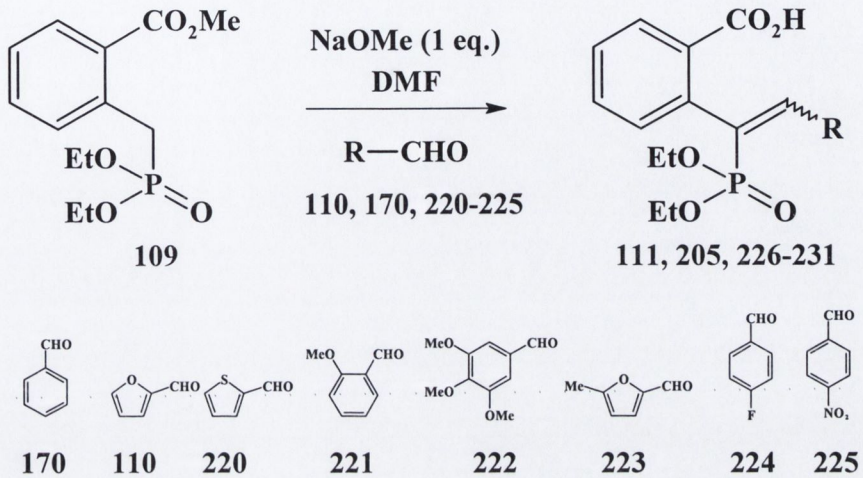


Scheme 3.19: Stereodependant reaction pathways of the intermediates **217a** and **217b**.

The yields of **207a** and **207b** were 45 % and 48 %, respectively, and the vinylphosphonates **216a** and **216b** obtained from the same reaction were isolated in 33 % and 40 % of the theoretical yields, respectively.

Only recently, Huddleston[61] repeated the experiments described by O'Neill[60] and then applied this reaction to a variety of other aromatic and heteroaromatic aldehydes **220-225**. The objective was to determine if the course of the reaction could be controlled by the electron-density on the aldehydic carbonyl group, which is influenced by the (hetero)aromatic rings and their electron-withdrawing or electron-releasing substituents.

When this reaction (**Scheme 3.20**) was attempted[61] with 2-furaldehyde **110**, benzaldehyde **170** or thiophene-2-carboxaldehyde **220** using almost the same reaction conditions described by O'Neill,[60] the corresponding vinylphosphonates **111**, **205** and **226** were obtained in low yields (**Table 3.2**).



Scheme 3.20: Horner-Emmons reactions between aldehydes and diethyl (2-carbomethoxy)benzylphosphonate **109** carried out by Huddleston.[61]

Table 3.2: Horner-Emmons reactions carried out by Huddleston[61] and yields obtained for the corresponding vinylphosphonates.

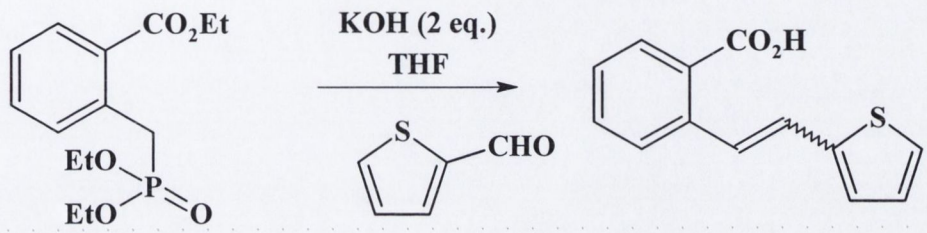
R	Aldehyde	Vinyl-phosphonate	[a]Yield (%)	[b]H. E. product
2-Furyl	**110**	**111**	11	Yes
Phenyl	**170**	**205**	11	Yes
2-Thienyl	**220**	**226**	10	Yes
o-Methoxyphenyl	**221**	**227**	0	No
3,4,5-Trimethoxyphenyl	**222**	**228**	0	No
2-(5-Methyl)furyl	**223**	**229**	0	No
p-Fluorophenyl	**224**	**230**	0	No
p-Nitrophenyl	**225**	**231**	0	No

[a] Yields given[61] are for the vinylphosphonates; [b] Horner-Emmons products found[61] in ethereal extracts.

The ethereal extracts of the product mixtures obtained from the reactions of the aldehydes **110**, **170** and **226** contained small amounts (<20 %) of the corresponding Horner-Emmons products together with some unreacted starting material. Reactions with the other aldehydes listed in **Table 3.2**, which are *o*-methoxybenzaldehyde **221**, 3,4,5-trimethoxybenzaldehyde **222**, 2-(5-methyl)furaldehyde **223**, *p*-fluoro-benzaldehyde **224** and *p*-nitrobenzaldehyde **225**, were not successful and none of the desired vinylphosphonates **227-231** could be isolated (**Scheme 3.20**). Extractions with diethyl ether before, and with ethyl acetate after acidification of these last five reaction mixtures yielded only the starting materials and some hydrolysed benzylic phosphonate **109**.

It was reported[61] that in the very first attempts most of the reactions between the aldehydes and the anion of the phosphonate **109** had failed, which was ascribed to residual water in the solvent, DMF. Problems were also encountered with the quality of the base, sodium methoxide, which from then on was freshly prepared from sodium and methanol prior to each reaction. However, despite some success in improving the reaction conditions, the vinylphosphonates could only be isolated in the few cases stated above and the yields were still poor (**Table 3.2**). Later on, it was suggested[61] that the stoichiometry of the base used in these experiments might have been responsible for the poor results. In his reaction, O'Neill[60] used a 1.2-molar excess of sodium methoxide (**Scheme 3.12, p105**), and Bodalski and Janecki[114] added 1.1-moles of LDA to the reaction mixture (**Scheme 3.18, p110**). Huddleston, however, employed stoichiometric quantities of base. An explanation for this dependency of the course of the reaction on the amount of base can be found in the mechanism which was proposed earlier[60] for the formation of the Stobbe-like products. Formation of the carbanion **204** in **Scheme 3.14 (p107)** requires one mole-equivalent of base. Lactonisation of the intermediate **113** regenerates a mole of base (methoxide ion), which is needed for the abstraction of the proton α to phosphorus to induce cleavage of the lactone ring of the intermediate **114**. Any competing reaction pathway that consumes methoxide ion, or quenching of the base by reaction with, *e.g.*, atmospheric CO_2, will clearly reduce the yield of the final product. From this point of view it seems reasonable that no or only small amounts of the vinylphosphonates had formed in the experiments carried out by Huddleston.

Besides the stoichiometry of the reagents used in this novel reaction, the solvent and the base were also found to play an important role. In a recent paper by Murty *et al.*,[115] a reaction of thiophene-2-carboxaldehyde **220**, similar to that of Huddleston, was described. In this experiment, however, the benzylphosphonate **232** was treated with two molar equivalents of potassium hydroxide and the reaction was carried out in dry tetrahydrofuran (THF). The work-up of the reaction mixture afforded 80 % of the theoretical yield of 2-[2'-(2"-thienyl)ethenyl]benzoic acid **233** (**Scheme 3.21**).

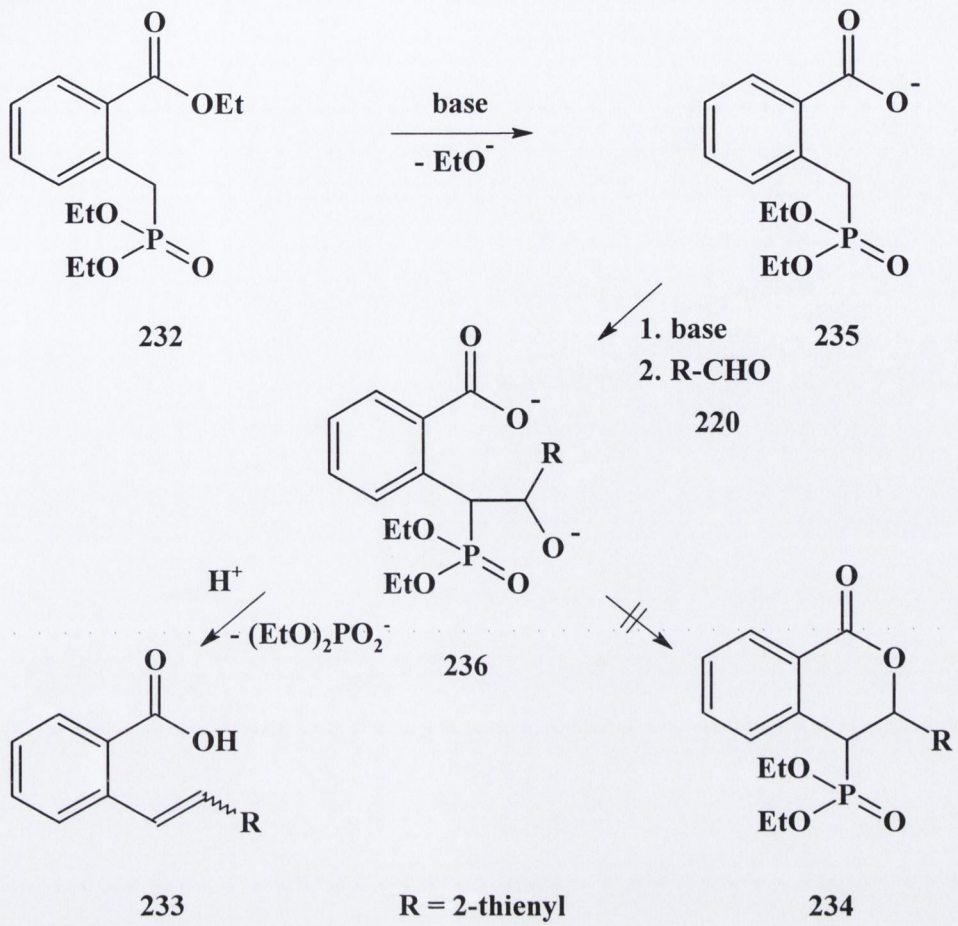


232 **220** **233 (80 %)**

Scheme 3.21: Reaction between the phosphonate **232** and thiophene-2-carboxaldehyde **220**.

The mechanism shown in **Scheme 3.22** might offer an explanation why in case of the experiment reported by Murty *et al.*[115] the formation of the lactone intermediate **234**, and hence, the formation of the vinylphosphonate **226** was not observed. If the carboxyl ester group of the phosphonate **232** is first hydrolysed to give the carboxylate anion **235**, which is then deprotonated at the benzylic position α to phosphorus and reacts with the aldehyde **220**, cyclisation of the resulting dianion **236** to give a lactone is very unlikely. Thus, it can be expected that the Stobbe-like pathway is not favoured and that the reaction will proceed *via* the "normal" Horner-Emmons pathway to give the alkene **233**.

Unfortunately, the geometry of the alkene **233** obtained from this reaction was not clarified by these authors,[115] and analytical data was only given for the (*Z*)-isomer of **233**, which was prepared[115] by an alternative method.



Scheme 3.22: Possible mechanism for the reaction described by Murty *et al.*[115]

As the experiment conducted by Murty *et al.*[115] is very closely connected with the present reaction, it was decided to repeat the olefination shown in **Scheme 3.21** using the exact same conditions reported by the authors. From a number of experiments, however, the intended acid **233** was never obtained in more than 12 % of the theoretical yield, the major product being recovered starting material **232**.

3.2 Synthetic strategy

On the basis of the results described above the objectives of this part of the Thesis might be achieved by

a) further investigating the reactions between the deprotonated phosphonate **109** and each of 2-furaldehyde **110**, benzaldehyde **170** and thiophene-2-carboxaldehyde **220** using an excess of base (two or three molar equivalents), and if necessary, changing the reaction conditions such as the solvent, base and reaction time in order to optimise the yields.

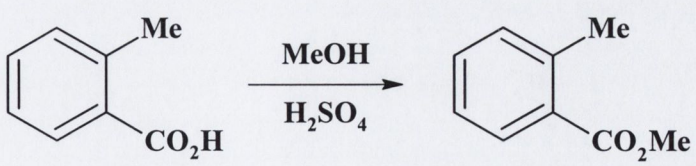
b) applying this new reaction to a broader variety of aldehydes in order to determine its scope and limitations.

3.3 Synthetic route towards diethyl (2-carbomethoxy)benzylphosphonate 109

The preparation of diethyl (2-carbomethoxy)benzylphosphonate **109**, which will be described in this Section, was carried out according to the experimental method reported by the above-mentioned authors.[60,61] This synthetic route consists of three steps of which the first one is the esterification of *o*-toluic acid **122**.

3.3.1 Preparation of methyl *o*-toluate 237

Methyl *o*-toluate **237** was obtained by refluxing a mixture of *o*-toluic acid **122**, methanol and sulfuric acid (**Scheme 3.23**).



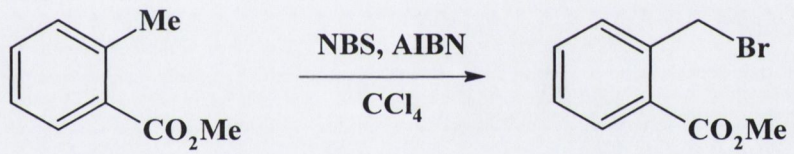
122 **237 (84 %)**

Scheme 3.23: Esterification of *o*-toluic acid **122**.

After distillation of the crude product, methyl *o*-toluate **237** was obtained as a yellow oil in 84 % yield and in good purity. The formation of the ester **237** was confirmed by proton nuclear magnetic resonance (^{1}H NMR) and infrared (IR) analysis. The ^{1}H NMR spectrum revealed a 3H-singlet at δ_H 2.50 ppm and a 3H-singlet at δ_H 3.90 ppm. The first signal corresponds to the set of protons of the methyl group attached to the benzene ring, and the second signal is assigned to the three methyl ester group protons. The aromatic proton signals resonate between δ_H 7.20-7.90 ppm. An absorption band at 1722 cm^{-1} in the IR spectrum corresponds to $\nu_{C=O}$ of the conjugated ester function.

3.3.2 Preparation of methyl 2-(bromomethyl)benzoate 238

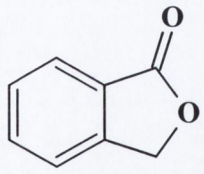
In the bromination step the ester **237** and a small excess of *N*-bromosuccinimide (NBS) were refluxed in distilled carbon tetrachloride for three hours. The addition of 2,2'-azobis-(2-methylpropionitrile) (AIBN) initiated the radical reaction **(Scheme 3.24)**.



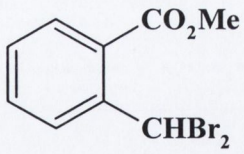
237 **238 (73-82 %)**

Scheme 3.24: Bromination of methyl *o*-toluate **237**.

This reaction yielded mostly the monobrominated ester **238**, on few occasions, however, significant amounts of one or two by-products had also formed. One of these compounds was phthalide **239**, a by-product that had also been isolated and identified by Huddleston[61] from his bromination mixtures. The lactone **239** could easily be identified as such by ^{1}H NMR analysis, the spectrum showing the same signals that were previously reported.[61] The other by-product was the dibromo ester **240**, representing a rather small fraction of the product mixture. In most cases, however, methyl 2-(bromomethyl)benzoate **238** was obtained as the major product in 73 to 82 % of the theoretical yield. An analytical sample of **238** was obtained by vacuum distillation.



239

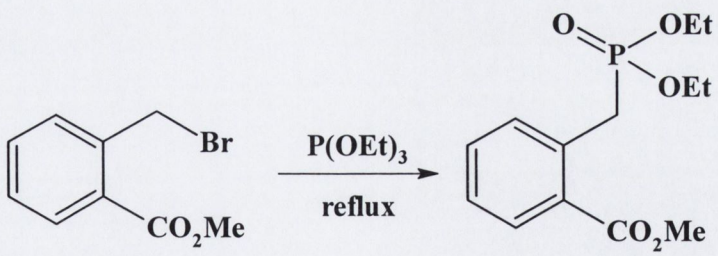


240

Formation of the benzylic bromide **238** was confirmed by ^{1}H NMR analysis, the data obtained being identical with the data reported by O'Neill[60] and by Huddleston.[61] A 3H-singlet at δ_H 3.90 ppm is assigned to the methyl ester protons and a 2H-singlet at δ_H 4.90 ppm corresponds to the two protons attached to the methylene carbon. The signals due to the aromatic protons are evident in the range of δ_H 7.30-8.00 ppm. The infrared spectrum of **238** shows an absorption band at 1720 cm^{-1}, which corresponds to $\nu_{C=O}$ of the ester group. Usually, the crude bromide **238** was subsequently reacted with triethyl phosphite in the following Arbuzov-reaction.

3.3.3 Preparation of diethyl (2-carbomethoxy)benzylphosphonate 109

According to **Scheme 3.25**, the Horner-Emmons reagent **109** was obtained from the Arbuzov-reaction between triethyl phosphite and the bromide **238**. The mixture was heated at reflux overnight, after which the phosphonate **109** was isolated and purified by vacuum distillation.



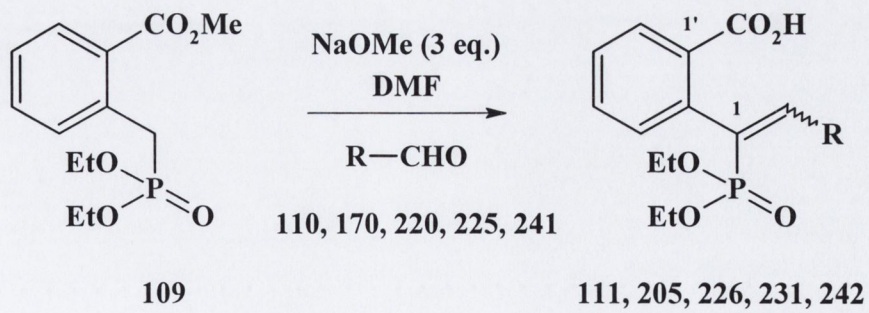
238 109 (90 %)

Scheme 3.25: Arbuzov reaction between methyl 2-(bromomethyl)benzoate **238** and triethyl phosphite.

The crude phosphonate **109** was obtained in 90 % yield and its formation was confirmed by ^{1}H NMR analysis. The spectrum reveals a 6H-triplet (J 7.0 Hz) centred at δ_H 1.14 ppm, which is assigned to the two sets of methyl protons of the phosphonate ester group. A 2H-doublet centred at δ_H 3.73 ppm with a coupling constant $^{2}J_{P\text{-}H}$ 22.6 Hz emanates from the methylene protons attached to the carbon next to phosphorus. The carboxyl ester group protons resonate as a 3H-singlet visible at δ_H 3.82 ppm, and a 4H-multiplet centred at δ_H 3.91 ppm is ascribed to the two sets of methylene protons of the phosphonate ester. In the IR spectrum of **109** an absorption band at 1722 cm^{-1} corresponds to $\nu_{C=O}$, and an absorption band at 1270 cm^{-1} corresponds to $\nu_{P=O}$.

3.4 First series of reactions under Horner-Emmons conditions

Initially, the procedure employed for the Horner-Emmons reactions of the phosphonate **109** was very similar to that which was used by O'Neill[60] and by Huddleston.[61] This included the preparation of fresh, solid sodium methoxide, to which a DMF solution of diethyl (2-carbomethoxy)benzylphosphonate **109** was added. Upon the addition of one of the aldehydes listed in **Table 3.2 (p112)** to this, the DMF solutions were stirred for one hour at room temperature and were then diluted with water and extracted with diethyl ether. The aqueous phases were then acidified and extracted with ethyl acetate, the latter extracts being expected to contain the desired, acidic vinylphosphonates. The only modification made to the original method was the amount of base used. Thus, instead of an equimolar amount, a three-fold excess of sodium methoxide was used (**Scheme 3.26**).



109 **111, 205, 226, 231, 242**

Scheme 3.26: First series of reactions under Horner-Emmons conditions.

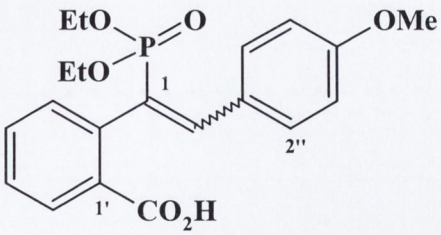
The selection of aldehydes (**Table 3.3**) for this first series of Horner-Emmons reactions was slightly different when compared to the aldehydes employed by Huddleston[61] (*cf.* **Table 3.2, p112**). *o*-Methoxybenzaldehyde **221** and *p*-fluorobenzaldehyde **224** were replaced by *p*-methoxybenzaldehyde **241**. 3,4,5-Trimethoxybenzaldehyde **222** and 2-(5-methyl)furaldehyde **223** were also not used in the present series of reactions. The results obtained from the experiments shown in **Scheme 3.26** are summarised in **Table 3.3**.

Table 3.3: Reactions between aldehydes and the deprotonated phosphonate **109**.

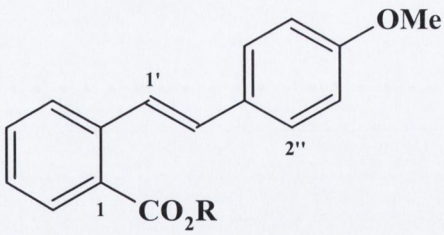
R	Aldehyde	Vinyl-phosphonate	[a]Yield (%)	[b]H. E. product
2-Furyl	**110**	**111**	13	Yes
Phenyl	**170**	**205**	10	Yes
2-Thienyl	**220**	**226**	13	Yes
p-Nitrophenyl	**225**	**231**	0	No
p-Methoxyphenyl	**241**	**242**	0	[c]Yes

[a] Yields of the vinylphosphonates; [b] Horner-Emmons products obtained from the ethereal extracts; [c] Most of the Horner-Emmons product was not obtained as the methyl ester **243**, but in its hydrolysed form, *i.e.*, the acid **244** (see also text).

The outcome of these reactions was very similar to that observed by Huddleston.[61] Extraction of the acidified reaction mixtures from the aldehydes **110**, **170** and **220** afforded the corresponding vinylphosphonates **111**, **205** and **226** in low yields (10-13 %) after recrystallisation (**Table 3.3**). From the work-up of the product mixture of the reaction with *p*-methoxybenzaldehyde **243** no vinylphosphonate **244** could be isolated. However, column chromatography of the ethyl acetate extracts of the acidified solution and recrystallisation of the solid obtained from the main fraction gave a substantial amount (30 %) of a crystalline compound. This was identified as the unsaturated acid **244** by ^{1}H NMR spectroscopy.



242



243 **R = Me**
244 **R = H**

In the ^{1}H NMR spectrum (**Figure 3.1**) of (*E*)-2-[2'-(*p*-methoxyphenyl)ethenyl]-benzoic acid **244** a doublet with a coupling constant of 16.4 Hz is centred at δ_H 7.13 ppm. This coupling constant compares favourably with the *J*-values observed[87] for vicinal vinylic protons of stilbenes with an (*E*)-configuration. The signal for the second vinyl proton (*H*-1') of **244** is found as a slightly obscured doublet centred at δ_H 7.79 ppm with the same coupling constant, *i.e.*, *J* 16.4 Hz.

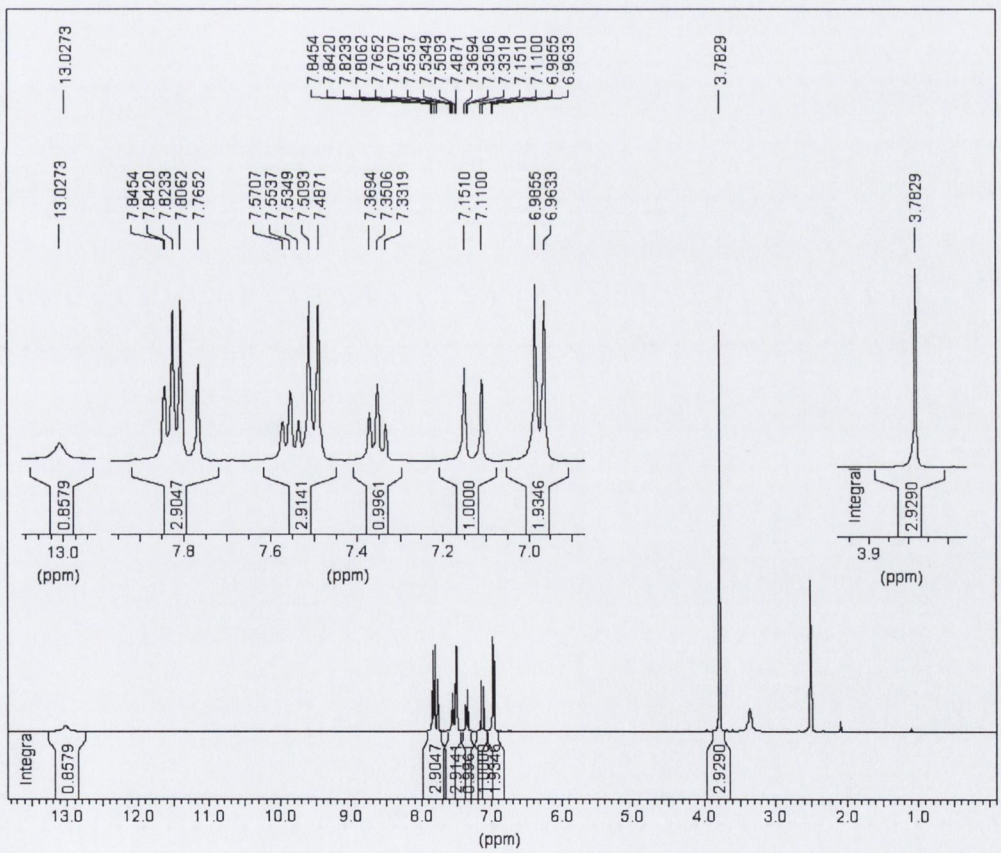


Figure 3.1: ^{1}H NMR spectrum of the *p*-methoxy-substituted stilbene **244**.

Two further characteristic signals are a broad 1H-singlet at δ_H 13.03 ppm and a sharp 3H-singlet at δ_H 3.78 ppm, which correspond to the carboxylic acid proton and the methyl protons of the methoxy group, respectively. Two 2H-doublets, centred at δ_H 7.50 and 6.97 ppm and both with *J* 8.9 Hz, are assigned to the four protons of the methoxy-substituted benzene ring. Two of the four resonances for the protons attached to the carboxyl-substituted benzene ring are evident as 1H-triplets (*J* 7.5 Hz) at δ_H 7.35 and 7.55 ppm. The proton in *para*-position to the carboxyl group corresponds to the signal further downfield. The other two aromatic proton signals for this ring appear between δ_H 7.78 and 7.88 ppm, overlap each other, and partially overlap the doublet due to the low-field vinylic proton. The assignment of the signals to the protons of the acid **244** was assisted by a ^{1}H-^{1}H COSY experiment. The IR spectrum of the acid **244** perfectly matched the IR data of the same compound reported by Zimmerman and Cutler.[116]

The other reaction, involving *p*-nitrobenzaldehyde **225**, produced only an intractable mixture, and the NMR spectra of the ethyl acetate extracts provided no evidence for the formation of the vinylphosphonate **231**.

Some of the ethereal extracts yielded small amounts (<20 %) of the "normal" Horner-Emmons products (**Table 3.3**), together with some starting materials. No effort to isolate the unsaturated esters was made, as the ^{1}H NMR spectra of the crude oils were almost identical to the data obtained by Huddleston[61] and gave sufficient proof for the formation of the Horner-Emmons products.

Besides the poor yields of the vinylphosphonates obtained from this first series of reactions, another problem was encountered when the recrystallised compounds **111**, **205** and **226** were analysed by means of ^{1}H NMR spectroscopy. A group of signals, which Huddleston[61] in his work had ascribed to residual ethanol from the recrystallisations, was visible at δ_H ~3.60 ppm, and these suggested that a reaction at the phosphonate group had occurred. This thought was substantiated by the integral values for the diethyl phosphonate ester group peaks (**Figure 3.2**) which were lower than expected. A reasonable explanation for this phenomenon is a transesterification reaction between sodium methoxide and the phosphonate esters (**Scheme 3.27**).

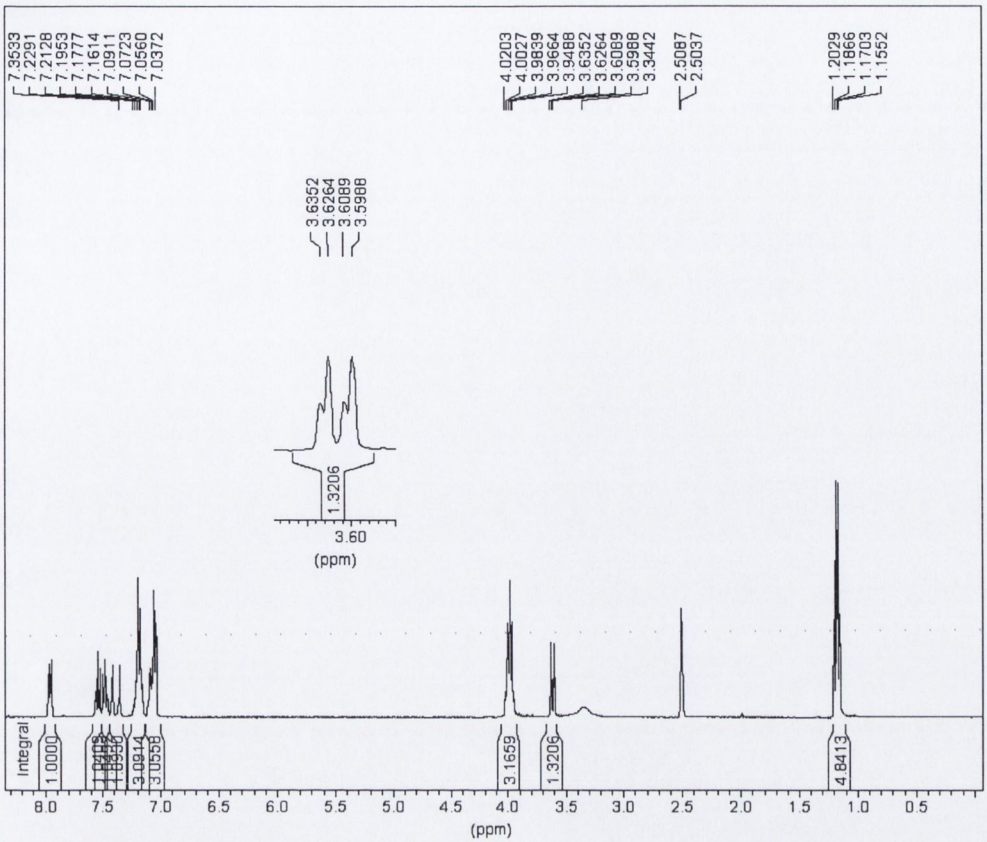
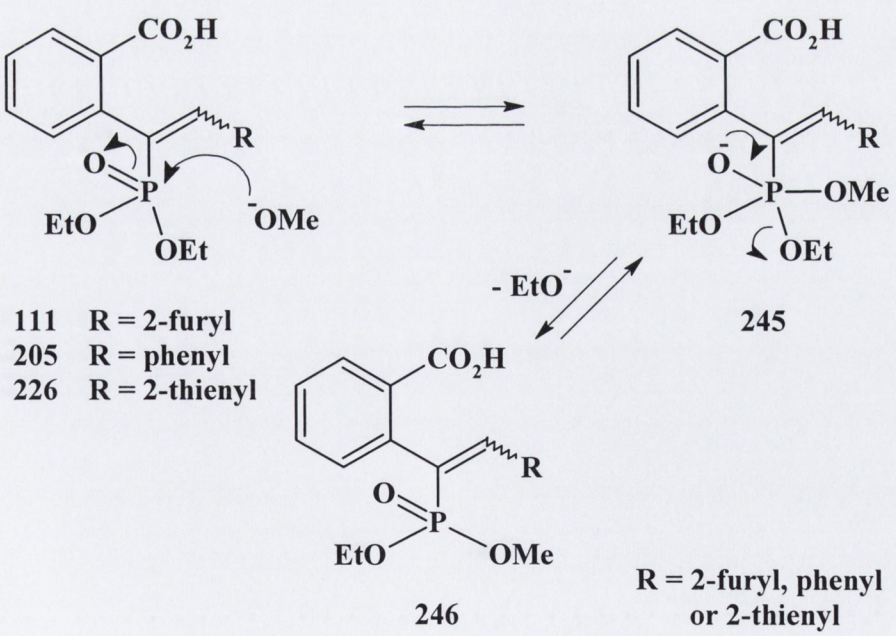
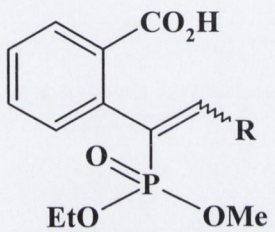


Figure 3.2: ^{1}H NMR spectrum of the contaminated vinylphosphonate **205** derived from benzaldehyde **170**.

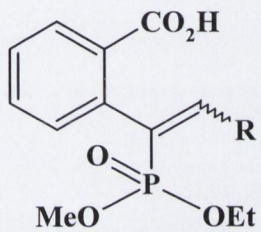


Scheme 3.27: Transesterification of the vinylphosphonates.

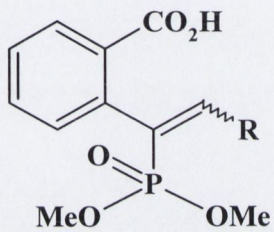
As shown in **Scheme 3.27**, the phosphonate function of the vinylphosphonates might have been attacked by methoxide ion to give the intermediate **245**, which then eliminated one of its ethoxy groups to yield the ethylmethyl phosphonate **246**. Further proof for this hypothesis was obtained from the multiplicity and *J*-values of the signals at δ_H ~3.60 ppm. Two doublets of almost equivalent chemical shifts were observed, each with a coupling constant of ~11 Hz, which is the expected $^3J_{P\text{-}H}$ value for methyl phosphonates.[117] The occurrence of two doublets can either be explained by reference to the tetrahedral shape of the phosphonate group, which leads to the two "enantiomers" **246a** and **246b** with slightly different chemical shifts for the methyl groups in the proton spectrum. Another explanation could be the formation of a mixture of the mono- and the dimethyl phosphonates **246** and **247**, respectively, producing the observed signals.



246a



246b



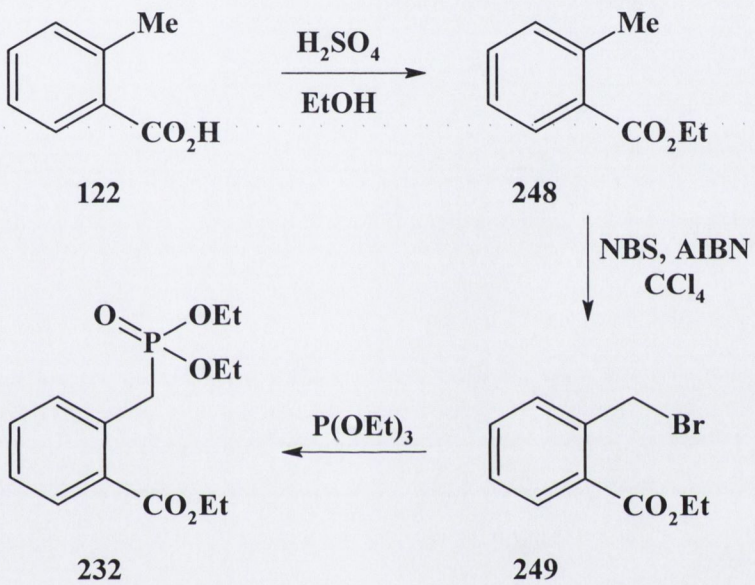
247

R = 2-furyl, phenyl or 2-thenyl

To avoid transesterification, the reaction between the phosphonate **109** and benzaldehyde **170** was repeated using three molar equivalents of freshly prepared sodium ethoxide as the base. The reaction was carried out under exactly the same conditions as described above and gave 27 % of the theoretical yield of the vinylphosphonate **205**. However, although very weak, the signal in the ^{1}H NMR spectrum due to methyl phosphonate groups was still present. Obviously, these must have formed in a transesterification reaction with methoxide ions, which were expelled from the carboxyl methyl ester groups in the formation step of the lactone ring. At this point it was decided to prepare a new Horner-Emmons reagent, *i.e.*, diethyl (2-carbo**ethoxy**)benzylphosphonate **232**, which would eliminate the problem of transesterification by employing exclusively ethoxide group-containing starting materials.

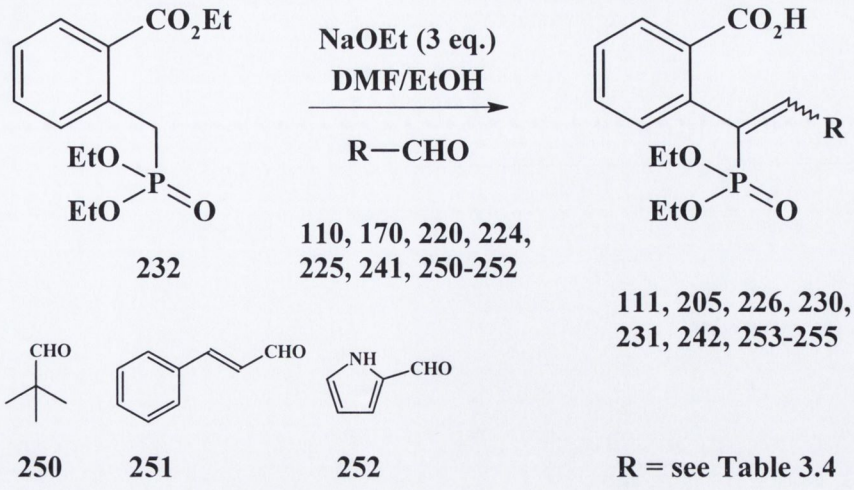
3.5 Second series of Horner-Emmons reactions

The phosphonate **232** was prepared by a synthetic route similar to that described in **Section 3.3 (p116)**. Instead of employing methanol, *o*-toluic acid **122** was heated in ethanol at boiling temperature to give the ethyl ester **248**. The latter was brominated to give the benzylic bromide **249**, which was finally converted into the phosphonate **232** by an Arbuzov reaction (**Scheme 3.28**). The products **248**, **249** and **232** were identified by means of ^{1}H NMR and IR analysis, and the spectra of these compounds showed signals identical to those which have been reported in the literature.[118]



Scheme 3.28: Synthetic route towards the diethyl phosphonate **232**.

Due to the low yields of the vinylphosphonates obtained in the first series of Horner-Emmons reactions described above, it was decided to alter the reaction conditions. As has been mentioned above, the solvent was found to have a strong influence on the course of the reaction. The proposed Stobbe-like mechanism for this reaction involves several charged intermediates hence, it appeared reasonable to enhance the stabilisation of the latter by employing a polar protic solvent, *e.g.*, ethanol, which at the same time would effectively not interfere with the base. Thus, in the second series of reactions the ethanolic solution containing the appropriate amount of sodium ethoxide was not evaporated to dryness, but the phosphonate **232**, dissolved in a little DMF, was added directly to this solution (**Scheme 3.29**).



Scheme 3.29: Second series of Horner-Emmons reactions.

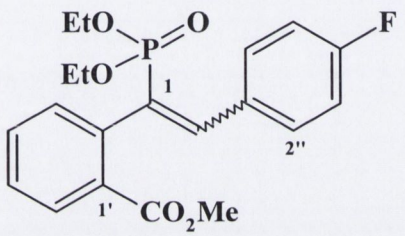
The first aldehyde to be reacted under these new conditions was benzaldehyde **170**, and the corresponding vinylphosphonate **205** was obtained in 89 % yield. Encouraged by this result, the same reaction was attempted with several more carbonyl compounds.

Table 3.4: Horner-Emmons reactions between aldehydes and the anion of **232**.

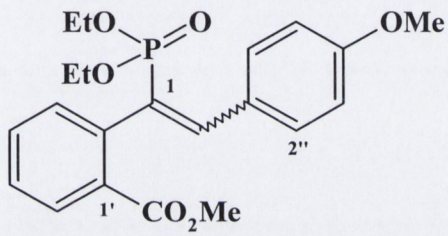
R	Aldehyde	Vinyl-phosphonate	[a]Yield (%)	[b]H.-E. product
2-Furyl	**110**	**111**	64	Yes
Phenyl	**170**	**205**	89	No
2-Thienyl	**220**	**226**	70	No
p-Fluorophenyl	**224**	**230**	87/[c]29	No
p-Nitrophenyl	**225**	**231**	0	No
p-Methoxyphenyl	**241**	**242**	79/[c]45	No
tert.-Butyl	**250**	**253**	0	No
(*E*)-Styryl	**251**	**254**	53	No
2-Pyrrolyl	**252**	**255**	0	No

[a] Yields of the purified vinylphosphonates; [b] Horner-Emmons products obtained from the ethereal extracts; [c] isolated as the corresponding methyl ester.

This selection of reactants (**Table 3.4**) included some compounds which had not been used in any of the previous series of reactions, namely trimethylacetaldehyde **250**, (*E*)-cinnamaldehyde **251** and 2-formylpyrrole **252**. As can be seen in **Table 3.4**, most of the reactions were successful, and the derived vinylphosphonates **111**, **205**, **226**, and **254** were obtained as crystalline solids in moderate to excellent yields. Initially, the experiments with 4-fluorobenzaldehyde **224** and 4-methoxy-benzaldehyde **241** yielded viscous oils, which contained mostly the desired phosphonic esters **230** and **242**, but which could not be purified satisfactorily. Thus, it was decided to convert the free acids **230** and **242** into the corresponding carboxylic methyl esters **256** and **257** by means of diazomethane. Each of these methylations afforded a crude, viscous product, which was chromatographed to yield the compounds **256** and **257**, respectively, as colourless oils.



256

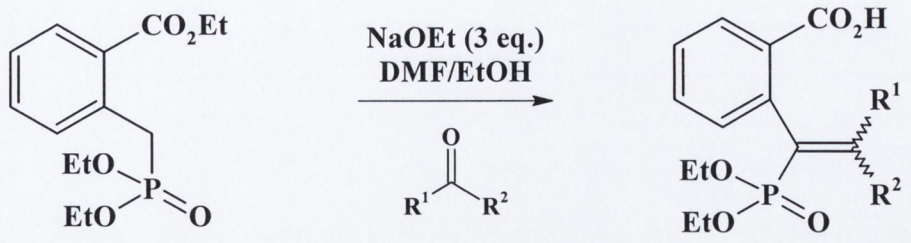


257

When 4-nitrobenzaldehyde **225**, trimethylacetaldehyde **250** or 2-formylpyrrole **252** were employed, the reaction shown in **Scheme 3.29** gave only intractable mixtures, from which neither the vinylphosphonates **231**, **253** and **255**, nor the corresponding Horner-Emmons products could be isolated. With its tertiary butyl group the aldehyde **250** might be too hindered to undergo this reaction. The unsuccessful outcome of the experiment involving pyrrole-2-carboxaldehyde **252** might be due to the poor electrophilicity of its formyl carbon atom.

The crude oils obtained from the ether extracts of all the reaction mixtures were analysed by ^{1}H NMR spectroscopy, but none of the "normal" Horner-Emmons products were found, the major content of these layers being unreacted aldehydes, the phosphonate **232** and residual DMF solvent. The only exception was the reaction of 2-furaldehyde **110**, where the ether extracts contained very small amounts (~10 %) of the ethyl (*E*)-2-[2'-(2''-furyl)ethenyl]benzoate **112**.

In another series of Stobbe-like reactions (**Scheme 3.30**), acetophenone **258a** and cyclopentanone **258b**, respectively, were reacted with deprotonated **232**.



232 **258a** **258b** **259a** **259b**

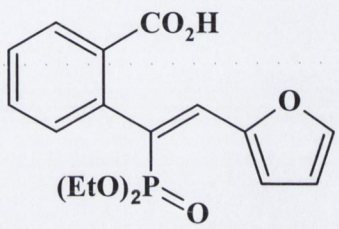
(a) R^1 = Me, R^2 = Ph
(b) R^1, R^2 = -$(CH_2)_4$-

Scheme 3.30: Stobbe-like reactions employing ketones **258a** and **258b**.

The first attempts of this reaction with **258a** or **258b**, respectively, were carried out under the same conditions that were used in the Stobbe-like reactions of the aldehydes, however, in the present case the ethyl acetate extracts of the acidified reaction mixtures afforded only (hydrolysed) starting material. In further experiments some of the reaction parameters, like the temperature, reaction time or the solvent, were changed. For example, on one occasion acetophenone **258a** and the deprotonated phosphonate **232** were heated at reflux in pure ethanol for four hours (compared to usually one hour of stirring at room temperature). Every single attempt with each of the two ketones proved unsuccessful, and there was no trace of the hypothetical vinylphosphonates **259a**/**259b** or the corresponding Horner-Emmons products.

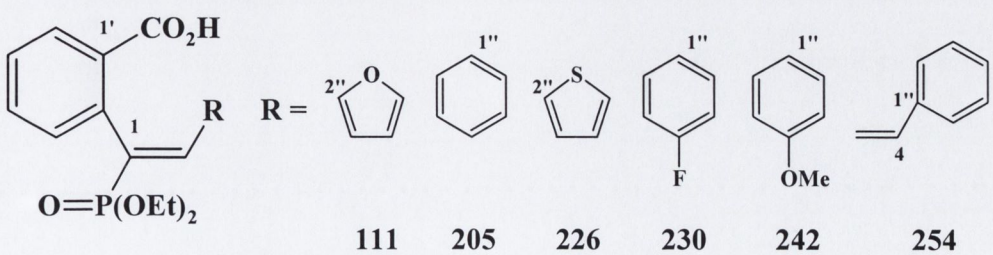
3.6 Characterisation of the vinylphosphonates

In this Section, the spectroscopic data of each of the novel vinylphosphonates **111**, **205**, **226**, **230** (Me ester **256**), **242** (Me ester **257**) and **254** will be analysed in detail in order to present firm evidence for the structures of these compounds. The structure of diethyl [1-(*o*-carboxyphenyl)-2-(2'-furyl)vinyl]phosphonate **111** was initially established by O'Neill,[60] and minor corrections to the interpretation of the NMR spectra were contributed by Huddleston.[61] Both authors assumed that this vinylphosphonate **111** must have a (*Z*)-configured alkene function. However, for reasons which will be given later on in this Section, it has now been deduced that the double bond of the vinylphosphonate **111** has the alternative (*E*)-configuration.



(*Z*)-111

The IR spectra of the vinylphosphonates **111**, **205**, **226**, **230**, **242** and **254** show very similar and characteristic patterns. Besides the absorptions for the carboxylic carbonyl group $\nu_{C=O}$ at ~1715 cm^{-1} (1726 cm^{-1} for the two methyl esters **256** and **257**) and for the aryl groups between 1550 and 1620 cm^{-1}, a pair of peaks at ~1058 cm^{-1} and at ~1029 cm^{-1} is evident in the spectra of the whole series of these novel compounds. These absorption bands most likely correspond to $\nu_{P\text{-}O\text{-}C}$. Another recognisable pattern in each IR spectrum consists of three strong absorptions which are found at ~1205, ~1160 and ~1140 cm^{-1} corresponding to $\nu_{P=O}$ of the phosphonate ester function and $\nu_{C=O}$ of the carboxyl group.



111 **205** **226** **230** **242** **254**

3.6.1 Characterisation of diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-(2'-furyl)vinyl]-phosphonate 111

As has been mentioned above, the spectroscopic features of one geometrical isomer of diethyl [1-(*o*-carboxyphenyl)-2-(2'-furyl)vinyl]phosphonate **111** have already been reported by O'Neill[60] and by Huddleston,[61] but due to newly obtained information on the geometry of the vinylphosphonate **111**, the ^{1}H NMR spectrum of the latter compound is discussed here again.

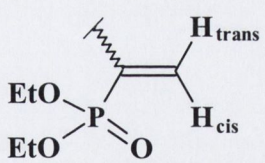
Two 3H-triplets, which partially overlap each other, resonate at δ_H 1.15 ppm and at δ_H 1.19 ppm and show a similar coupling constant of 7.0 Hz. These signals represent the methyl groups of the phosphonate ester. Due to the tetrahedral shape of the phosphonate group with phosphorus in its centre, the two methyl groups are non-equivalent, resulting in the appearance of two triplets with slightly different chemical shifts. The four methylene protons of the phosphonate ester function appear as a multiplet between δ_H 3.90 and 4.05 ppm. The carboxylic acid proton resonates at δ_H 12.70 ppm. A 1H-doublet at δ_H 5.86 ppm with *J* 3.5 Hz, a 1H-doublet of doublets centred at δ_H 6.40 ppm with J_1 3.5 and J_2 2.0 Hz, and an apparent singlet (partially obscured) resonating at δ_H 7.59 ppm correspond to the three furyl protons *H*-3", *H*-4" and *H*-5", respectively. These assignments were confirmed by ^{1}H-^{1}H COSY experiment. The 1H-doublet with *J* 7.5 Hz at δ_H 7.97 ppm is assigned to the proton attached to *C*-6' in the benzene ring. This signal is coupled to a 1H-triplet (*J* 7.5 Hz) at δ_H 7.50 ppm which arises from *H*-5'. Another 1H-triplet at δ_H 7.61 ppm with a coupling constant of *J* 7.5 Hz represents *H*-4', and a 1H-doublet (*J* 7.5 Hz) at δ_H 7.18 ppm is due to the proton on *C*-3'. The 1H-doublet centered at δ_H 7.18 ppm with $^{3}J_{P\text{-}H}$ 23.6 Hz can be unambiguously assigned to the vinyl proton. All proton resonances of this compound **111** together with their assignments are also listed in **Table 3.5**.

Table 3.5: Chemical shifts δ_H of the furyl-substituted vinylphosphonate **111**.

Assignment	Chemical Shift δ_H (ppm)	Multiplicity and *J*-Value (Hz)
OCH_2CH_3	1.15	t, 7.0
OCH_2CH_3	1.19	t, 7.0
$2\times OCH_2CH_3$	3.90-4.05	m
H-3" furyl	5.86	d, 3.5
H-4" furyl	6.40	dd, 3.5 and 2.0
H-2	7.18	d, 23.6
H-3'	7.18	d, 7.5
H-5'	7.50	d, 7.8
H-4' and *H*-5" furyl	7.55-7.67	m
H-6'	7.97	d, 7.5
CO_2H	12.70	s

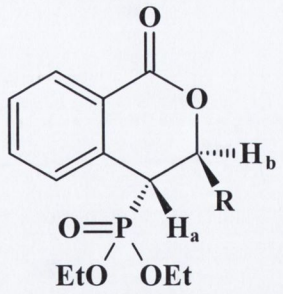
The ^{31}P-^{1}H coupling constant of the doublet due to the vinylic proton provides valuable information on the geometry of the double bond. A number of studies on this subject have been published in the literature.[108,110,119-122] The values observed for the relevant coupling constants by Xu *et al.*[121] are shown in **Table 3.6**.

Table 3.6: Vicinal coupling constants[121] between phosphorus and vinyl hydrogens in α,β-unsaturated phosphonates.



	$^{3}J_{P\text{-}H}$
H_{cis}	**10-30 Hz**
H_{trans}	**30-50 Hz**

According to this data it must be concluded, contrary to O'Neill[60] and to Huddleston,[61] that the vinyl proton of **111** ($^{3}J_{P\text{-}H}$ 23.6) is in the *cis*-position relative to the phosphonate ester group, and hence, that the furan ring is in the *trans*-position. This conclusion is also supported by the proposed geometry of the lactone intermediate **260a**.



260 **R = aryl, subst. aryl, etc.**
260a **R = 2-furyl**

Due to the steric demands of the furan ring and the phosphonate ester group, the lactone **260a** shown above is probably the sterically most favoured isomer. When the double bond of the final product is formed from the lactone isomers **260a**, respectively, it appears reasonable that the resulting vinylphosphonate **111** should predominantly, if not exclusively, be present with the vinyl proton H_b in *cis*-position to the phosphonate ester function.

In the carbon NMR spectrum of the furyl-substituted alkene **111** a signal at δ_C 167.37 ppm corresponds to the carbon of the acid function. A doublet resonating at δ_C 16.13 ppm with a coupling constant of $^2J_{P\text{-}C}$ 6.8 Hz is assigned to the methyl carbons. The two methylene carbons of the ethyl ester groups are not chemically equivalent and appear as two doublets ($^2J_{P\text{-}C}$ 5.8 Hz) at δ_C 61.88 and 61.41 ppm, respectively. From a ^{13}C-^1H COSY experiment the following assignments were made, and the obtained data is summarised in **Table 3.7**. The three tertiary furyl carbons are evident at δ_C 144.59 (*C*-5"), 113.63 (*C*-3") and 112.13 (*C*-4") ppm. A doublet ($^2J_{P\text{-}C}$ 11.7 Hz) at δ_C 128.29 ppm arises from the vinyl carbon *C*-2. The *C*-4' carbon of the benzene ring resonates at δ_C 132.13, a signal due to *C*-6' appears at δ_C 130.50 and a singlet at δ_C 128.01 ppm is assigned to *C*-5'. Coupling with phosphorus splits the signal of *C*-3' at δ_C 130.34 ppm into a doublet ($^3J_{P\text{-}C}$ 4.9 Hz). All four remaining quaternary carbons show coupling to phosphorus. Thus, a doublet with a coupling constant of 187.6 Hz at δ_C 127.98 ppm is assigned to the vinyl carbon *C*-1 next to phosphorus, while another doublet with $^3J_{P\text{-}C}$ 4.9 Hz, resonating at δ_C 131.00 ppm, corresponds to *C*-1' of the benzene ring. The other two carbons appear as doublets at δ_C 136.59 ($^2J_{P\text{-}C}$ 5.8 Hz, *C*-2') and δ_C 150.62 ($^3J_{P\text{-}C}$ 27.2 Hz, *C*-2") ppm.

Table 3.7: Chemical shifts δ_C of the furyl-substituted vinylphosphonate **111**.

Assignment	Chemical Shift δ_H (ppm)	Multiplicity and *J*-Value (Hz)
2×OCH_2CH_3	16.13	d, 6.8
OCH_2CH_3	61.41	d, 5.8
OCH_2CH_3	61.88	d, 5.8
C-4"	112.13	s
C-3"	113.63	s
C-1	127.98	d, 187.6
C-5'	128.01	s
C-2	128.29	d, 11.7
C-3'	130.34	d, 4.9
C-6'	130.50	s
C-1'	131.00	d, 4.9
C-4'	132.13	s
C-2'	136.59	d, 5.8
C-5"	144.59	s
C-2"	150.62	d, 27.2
CO_2H	167.37	s

3.6.2 Characterisation of diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-phenylvinyl]-phosphonate 207

The assignment of the signals in the ^1H NMR spectrum (**Figure 3.3**) of diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-phenylvinyl]phosphonate **207** was assisted by ^1H-^1H COSY, TOCSY and n.O.e experiments. The methyl protons appear as two overlapping 3H-triplets (*J* 7.0 Hz) at δ_H 1.16 and δ_H 1.18 ppm. An apparent 4H-quintet with *J* 7.0 Hz, centred at δ_H 3.98 ppm, corresponds to the methylene protons of the phosphonate ester group. The 1H-singlet at δ_H 12.80 ppm represents CO_2H. A 1H-doublet with *J* 7.5 Hz at δ_H 7.95 ppm corresponds to *H*-6', and a 1H-triplet with *J* 7.0 Hz, which resonates at δ_H 7.54 ppm, arises from the proton on *C*-4'.

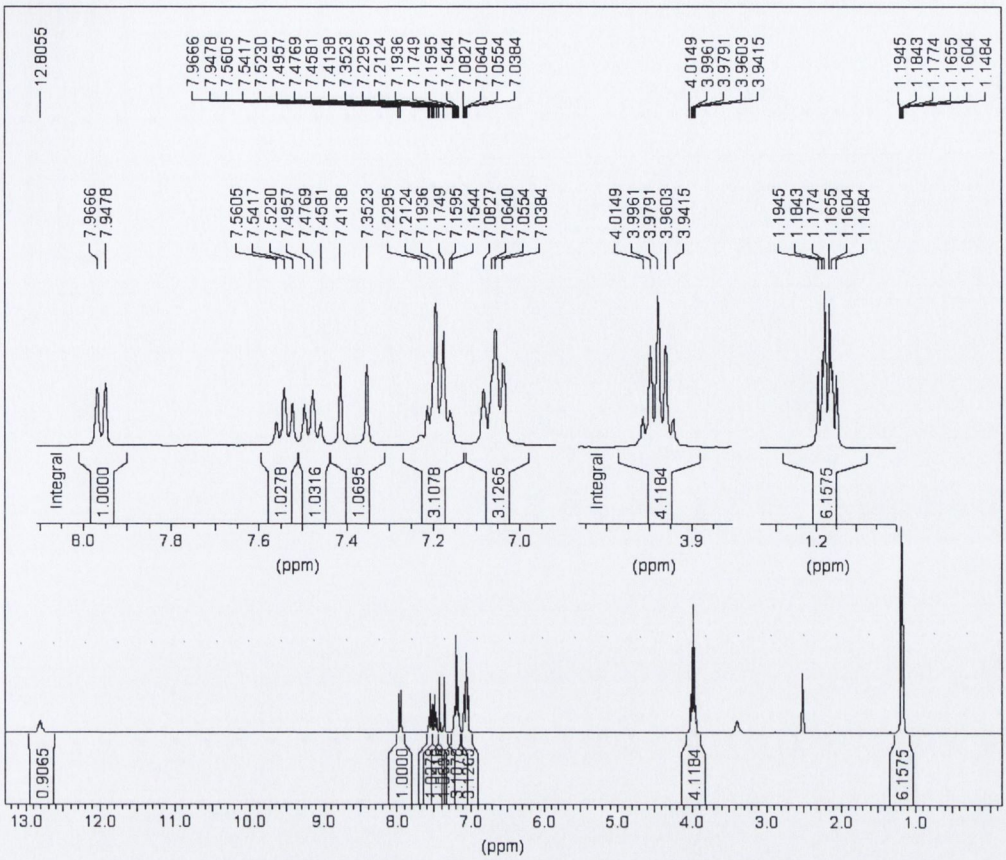


Figure 3.3: Proton NMR spectrum of the vinylphosphonate **205**.

Another 1H-triplet at δ_H 7.48 ppm with a coupling constant of 7.5 Hz corresponds to *H*-5'. A doublet centred at δ_H 7.38 ppm, which has a coupling constant of 24.6 Hz, is assigned to the vinyl proton. According to the data shown in **Table 3.6 (p131)**, the $^3J_{P\text{-}H}$-value observed in the present case confirms again a *cis* P-H vicinal relationship. A TOCSY experiment revealed a 1H-doublet at δ_H 7.07 ppm with *J* 8 Hz, which is due to *H*-3'. An n.O.e. experiment was carried out, where the NMR sample was irradiated with a frequency corresponding to the signal of the vinyl proton, which caused the appearance of a 2H-doublet with *J* 8 Hz at δ_H 7.04 ppm. This signal, which overlaps with the 1H-doublet centred at δ_H 7.07 ppm, was assigned to the *ortho*-protons of *C*-2" and *C*-6" of the unsubstituted benzene ring. A more downfield multiplet at δ_H 7.15-7.25 ppm arises from the three remaining aromatic protons, *i.e.*, *H*-3", *H*-4" and *H*-5". **Table 3.8** contains the chemical shifts δ_H observed for the vinylphosphonate **205**, and the corresponding assignments.

Table 3.8: Chemical shifts δ_H of the phenyl-substituted vinylphosphonate **205**.

Assignment	Chemical Shift δ_H (ppm)	Multiplicity and *J*-Value (Hz)
OCH_2CH_3	1.16	t, 7.0
OCH_2CH_3	1.18	t, 7.0
$2\times OCH_2CH_3$	3.98	app. quintet, 7.0
H-3', *H*-2" and *H*-6"	7.00-7.13	m
H-3", *H*-4" and *H*-5"	7.15-7.25	m
H-2	7.38	d, 24.6
H-5'	7.48	d, 7.5
H-4'	7.54	d, 7.0
H-6'	7.95	d, 7.5
CO_2H	12.80	s

Assignment of the carbons of the vinylphosphonate **205** was attempted using ^{13}C-^{1}H COSY analysis, but was difficult due to overlapping signals. A doublet $^{3}J_{P\text{-}C}$ 5.8 Hz corresponding to the methyl carbons appears at δ_C 16.11 ppm, and the methylene carbons are represented as two doublets ($^{2}J_{P\text{-}C}$ 5.8 Hz) centred at δ_C 61.38 and 61.83 ppm. The signal due to *C*=O resonates at δ_C 167.70 ppm. Further easily distinguishable signals are a doublet ($^{2}J_{P\text{-}C}$ 9.7 Hz) at δ_C 140.26 ppm (PC=*C*), and two singlets at δ_C 132.25 (*C*-4') and 128.02 (*C*-5') ppm, respectively. The ^{13}C-^{1}H COSY spectrum shows that an apparent singlet at δ_C 130.45 ppm corresponds to *C*-3' and *C*-6'. The five tertiary carbons of the second benzene ring resonate at δ_C 128.28 (*C*-3", *C*-5"), 128.81 (*C*-4") and 129.69 (*C*-2", *C*-6") ppm. A doublet with $^{3}J_{P\text{-}C}$ 3.9 Hz, resonating at δ_C 131.79 ppm, represents the benzene ring carbon *C*-1' adjacent to the carboxyl group, and another doublet ($^{1}J_{P\text{-}C}$ 182.7 Hz) at δ_C 131.83 ppm is assigned to the vinyl carbon *C*-1. Two more doublets are found at δ_C 134.78 ($^{3}J_{P\text{-}C}$ 22.4 Hz, *C*-1") and 136.52 ($^{3}J_{P\text{-}C}$ 6.8 Hz, *C*-2') ppm. The chemical shifts δ_C corresponding to the carbons of the phenylvinylphosphonate **205** are presented in **Table 3.9**.

Table 3.9: Chemical shifts δ_C of the phenyl-substituted vinylphosphonate **205**.

Assignment	Chemical Shift δ_C (ppm)	Multiplicity and *J*-Value (Hz)
$2\times OCH_2CH_3$	16.11	d, 5.8
OCH_2CH_3	61.38	d, 5.8
OCH_2CH_3	61.83	d, 5.8
C-5'	128.02	s
C-3"and *C*-5"	128.28	s
C-4"	128.81	s
C-2"and *C*-6"	129.69	s
C-3' and *C*-6'	130.45	s
C-1'	131.79	d, 3.9
C-1	131.83	d, 182.7
C-4'	132.25	s
C-1"	134.78	d, 22.4
C-2'	136.52	d, 6.8
C-2	140.26	d, 9.7
CO_2H	167.70	s

3.6.3 Characterisation of diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-(2'-thienyl)-vinyl]phosphonate 226

In the ^{1}H NMR spectrum of diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-(2'-thienyl)vinyl]-phosphonate **226** the following signals are observed. Two overlapping 3H-triplets at δ_H 1.15 and 1.19 ppm arise from the methyl protons, and a 4H-multiplet at δ_H 3.90-4.10 ppm corresponds to the methylene protons of the phosphonate ester group. The signal due to the acid proton is evident at δ_H 12.71 ppm. An apparent 1H-triplet at δ_H 6.99 ppm with a coupling constant of 4.4 Hz is assigned to *H*-4". The proton attached to *C*-3" is represented by a 1H-doublet at δ_H 7.33 ppm with *J* 3.4 Hz, and another 1H-doublet at δ_H 7.46 ppm with a coupling constant of 4.8 Hz corresponds to the remaining thienyl proton at *H*-5".

The signals due to *H*-6' and *H*-3' appear as doublets, each with *J* 7.5 Hz, at δ_H 8.01 and 7.18 ppm, respectively. A 3H-multiplet observed between δ_H 7.50 and 7.70 ppm was resolved by TOCSY, n.O.e. and ^{1}H-^{1}H COSY experiments. Thus, a doublet with a coupling constant of $^3J_{P\text{-}H}$ 23.2 Hz due to the vinylic proton and two 1H-triplets (*J* 7.5 Hz) at δ_H 7.64 and 7.55 ppm corresponding to *H*-4' and *H*-5', respectively, were identified. The ^{31}P-^{1}H coupling constant of 23.2 Hz confirms again the presence of an *E*-configured double bond. **Table 3.10** contains the chemical shifts δ_H of the observed peaks arising from the protons of the thienyl derivative **226**.

Table 3.10: Chemical shifts δ_H of the thienyl-substituted vinylphosphonate **226**.

Assignment	Chemical Shift δ_H (ppm)	Multiplicity and *J*-Value (Hz)
OCH_2CH_3	1.15	t, 7.2
OCH_2CH_3	1.19	t, 7.5
$2\times OCH_2CH_3$	3.90-4.10	m
H-4"	6.99	app. t, 4.4
H-3'	7.18	d, 7.5
H-3"	7.33	d, 3.4
H-5"	7.46	d, 4.8
H-2, *H*-4' and *H*-5'	7.50-7.70	m
H-6'	8.01	d, 7.5
CO_2H	12.71	s

The carbon spectrum was assigned as follows. A doublet with $^3J_{P\text{-}C}$ 5.8 Hz at δ_C 16.14 ppm corresponds to the methyl group and the two doublets ($^2J_{P\text{-}C}$ 4.9 Hz and $^2J_{P\text{-}C}$ 5.8 Hz) centred at δ_C 61.29 and 61.79 ppm are due to the methylene carbons. The tertiary carbons of the thienyl ring are evident as singlets at δ_C 126.57 (*C*-4"), 130.55 (*C*-5") and 132.84 (*C*-3") ppm. A doublet with $^2J_{P\text{-}C}$ 12.6 Hz, which is due to the vinyl carbon *C*-2, is found at δ_C 134.07 ppm.

The four tertiary carbons of the benzene ring resonate at δ_C 128.70 (*C*-5'), 130.95 (*C*-6'), 131.29 (d, $^3J_{P\text{-}C}$ 4.9 Hz, *C*-3') and 132.63 (*C*-4') ppm, and the signal at δ_C 167.18 ppm is unambiguously assigned to the carboxylic acid carbon. Due to overlapping signals in the ^{13}C spectrum, assignment of the quaternary carbons might not be completely accurate. For example, one peak is located at δ_C 126.83 ppm, which is believed to be one part of the expected doublet corresponding to the vinyl carbon *C*-1. The other part of the doublet, which would have a coupling constant $^1J_{P\text{-}C}$ of 188.0 Hz, overlaps with the signal at δ_C 128.70 ppm, which is assigned to *C*-5'. Another doublet with $^3J_{P\text{-}C}$ 4.9 Hz resonates at δ_C 131.71 ppm and represents *C*-1' of the benzene ring. The signal due to the adjacent carbon *C*-2' also appears as a doublet at δ_C 135.72 ppm and has a *J*-value of 6.8 Hz. The last signal is a doublet ($^3J_{P\text{-}C}$ 25.3 Hz) at δ_C 138.41 ppm, and is ascribed to *C*-2" (**Table 3.11**).

Table 3.11: Chemical shifts δ_C of the thienylvinylphosphonate **226**.

Assignment	Chemical Shift δ_C (ppm)	Multiplicity and *J*-Value (Hz)
$2\times OCH_2CH_3$	16.14	d, 5.8
OCH_2CH_3	61.29	d, 4.9
OCH_2CH_3	61.79	d, 5.8
C-4"	126.57	s
C-1	127.76	d, 188.0
C-5'	128.70	s
C-5"	130.55	s
C-6'	130.95	s
C-3'	131.29	d, 4.9
C-1'	131.71	d, 4.9
C-4'	132.63	s
C-3"	132.84	s
C-2	134.07	d, 12.6
C-2'	135.72	d, 6.8
C-2"	138.41	d, 25.3
CO_2H	167.18	s

3.6.4 Characterisation of crude diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-(*p*-fluorophenyl)vinyl]phosphonate 230 and its purified methyl ester 256

A sufficiently pure sample of the fluoro-derivative **230** was analysed by NMR spectroscopy. As has been observed in the proton spectra of the preceding vinylphosphonates, the signals due to the two sets of methyl protons of the phosphonate group of compound **230** have slightly different chemical shifts. In the ^{1}H NMR spectrum of **230** (**Table 3.12**) these two triplets (*J* 7.2 Hz) are even further separated, resonating at δ_H 1.17 and 1.31 ppm. The two 2H-multiplets corresponding to the methylene protons are also separated enough that no overlapping is observed. The first of these two signals is a complex multiplet, which ranges between δ_H 3.98 and 4.10 ppm, and the second CH_2–group is represented by an apparent quintet centred at δ_H 4.16 ppm with *J* 7.2 Hz. The two protons *ortho* to fluorine are evident as a 2H-apparent triplet with *J* 8.6 Hz, which is centred at δ_H 6.82 ppm, while *H*-2" and *H*-6", being *meta* to fluorine, resonate as a 2H-doublet of doublets with J_1 8.9 Hz and J_2 5.5 Hz at δ_H 7.00 ppm. Two doublets with *J* 7.5 Hz are found at δ_H 8.08 and 7.13 ppm, respectively, corresponding to *H*-6' and *H*-3'. The signals due to the vinyl proton and the protons attached to *C*-4' and *C*-5' appear as a multiplet in the range of δ_H 7.43-7.55 ppm.

Table 3.12: Chemical shifts δ_H of the vinylphosphonate **230**.

Assignment	Chemical Shift δ_H (ppm)	Multiplicity and *J*-Value (Hz)
OCH_2CH_3	1.17	t, 7.2
OCH_2CH_3	1.31	t, 7.2
OCH_2CH_3	3.98-4.12	m
OCH_2CH_3	4.16	app. quintet, 7.2
H-5"	6.82	app. t, 8.5
H-2" and *H*-6"	7.00	dd, 8.9 and 5.5
H-3'	7.13	d, 7.5
H-2, *H*-4' and *H*-5'	7.43-7.55	m
H-6'	8.08	d, 7.5

The coupling constant of the doublet due to the vinyl proton was determined in a TOCSY experiment and has a *J*-value of 24.0 Hz, which again confirms the presence of an *E*-configured double bond.

Assignment of the signals in the ^{13}C spectrum of the vinylphosphonate **230** (**Table 3.13**) was assisted by a ^{13}C-^{1}H COSY experiment. The singlet at δ_C 169.29 ppm is assigned to CO_2H. Unlike the other vinylphosphonates discussed so far, the carbons of the methyl groups appear as two doublets ($^{3}J_{P\text{-}C}$ 6.8 Hz) centred at δ_C 15.68 and 15.78 ppm, respectively. Two doublets due to the methylene carbons have a coupling constant of 5.8 Hz and resonate at δ_C 62.33 and 62.69 ppm.

Table 3.13: Chemical shifts δ_C of the vinylphosphonate **230**.

Assignment	Chemical Shift δ_C (ppm)	Multiplicity and *J*-Value (Hz)
OCH_2CH_3	15.68	d, 6.8
OCH_2CH_3	15.78	d, 6.8
OCH_2CH_3	62.33	d, 5.8
OCH_2CH_3	62.69	d, 5.8
C-3" and *C*-5"	114.95	d, 22.2
C-5'	127.93	d, 2.9
C-1	129.36	d, 187.6
C-3'	130.06	d, 4.9
C-1"	130.34	dd, 22.8 and 3.4
C-6'	131.01	s
C-2" and *C*-6"	131.50	d, 8.7
C-4'	132.15	s
C-2'	135.20	d, 6.8
C-2	140.57	d, 10.7
C-4"	162.34	d, 250.7
CO_2H	169.29	s

The tertiary carbons of the fluoro-substituted benzene ring are represented by two doublets, the first doublet with $^{2}J_{C\text{-}F}$ 22.2 Hz appearing at δ_C 114.95 (*C*-3", *C*-5"), and the second doublet, with a coupling constant of $^{3}J_{C\text{-}F}$ 8.7 Hz, resonating at δ_C 131.50 (*C*-2", *C*-6") ppm. One doublet (*J* 2.9 Hz) centred at δ_C 127.93 ppm is assigned to *C*-5' of the benzene ring, and another doublet centred at δ_C 130.06 ppm with $^{3}J_{P\text{-}C}$ 4.9 Hz corresponds to *C*-3'. Two singlets at δ_C 131.01 and 132.15 ppm arise from *C*-6' and *C*-4', respectively, while a doublet centred at δ_C 140.57 ppm ($^{2}J_{P\text{-}C}$ 10.7 Hz) represents the vinyl carbon *C*-2. Again, the assignment of the quaternary carbons is difficult due to overlapping signals. However, a doublet resonating at δ_C 162.34 ppm, which has a coupling constant of 250.7 Hz due to fluorine, is unambiguously assigned to *C*-4", and another doublet ($^{3}J_{P\text{-}C}$ 6.8 Hz) appears at δ_C 135.20 ppm and emanates from *C*-2'. One part of a doublet, which arises from *C*-1, resonates at δ_C 128.43 ppm. The other part of this doublet is partially obscured by a double doublet centred at δ_C 130.34 ppm. The latter signal, which is split into a doublet of doublets due to coupling with the fluorine and the phosphorus nuclei, can unambiguously be assigned to *C*-1". The observed coupling constants for this signal have a magnitude of 22.8 and 3.4 Hz. With regard to the spectra of the other vinylphosphonates, it can be assumed that the signal due to the *C*-1' carbon resonates at ~δ_C 131.50 ppm, but is covered by the doublet which arises from *C*-2" and *C*-6".

The NMR experiments, which were carried out on the analytically pure methylated derivative **256**, provided data which was, not surprisingly, very similar to the data obtained from the free acid **230**. The key feature of the ^{1}H NMR spectrum of **256** (**Figure 3.4**) is a 3H-singlet at δ_H 3.78 ppm due to the carbomethoxy protons, and in the ^{13}C NMR spectrum a singlet at δ_C 51.57 ppm is observed, which arises from CH_3 of the carboxy ester function. The chemical shifts δ_H and coupling constants of the signals observed in the proton NMR spectrum of **256** are listed in **Table 3.14**, and the spectroscopic data obtained from the carbon NMR experiment is shown in **Table 3.15**.

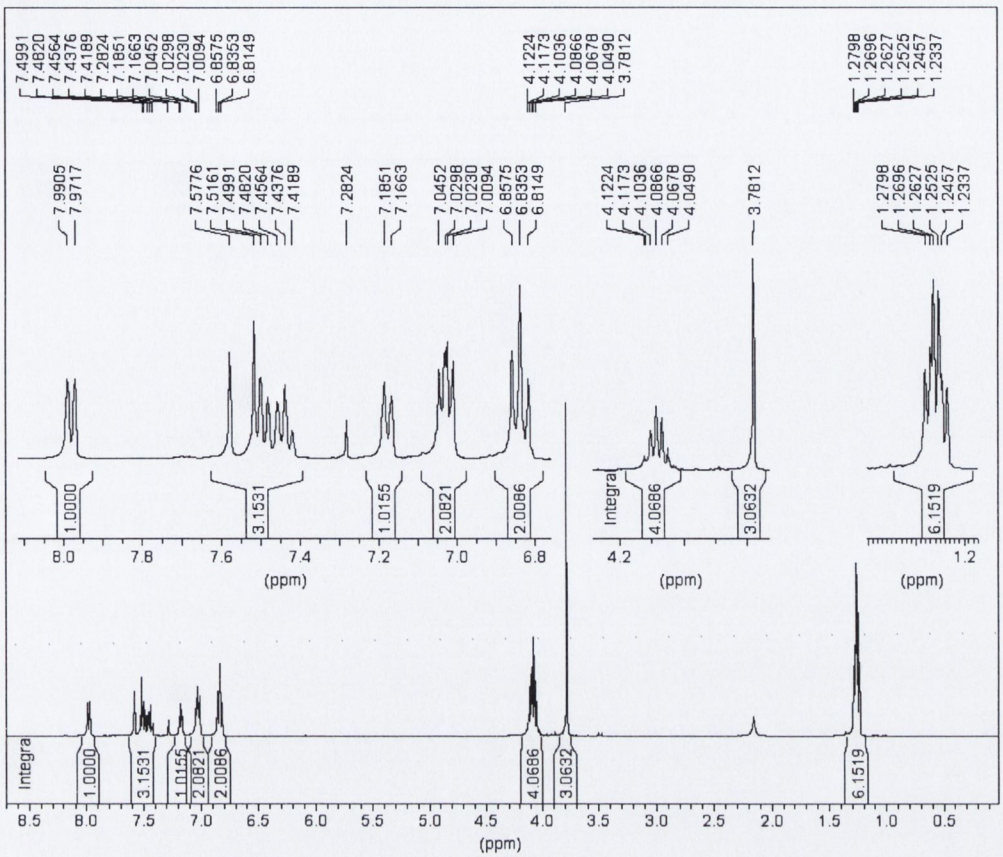


Figure 3.4: ^{1}H NMR spectrum of the ester **256** of the vinylphosphonate **230**.

Table 3.14: Chemical shifts δ_H of the methyl ester **256**.

Assignment	Chemical Shift δ_H (ppm)	Multiplicity and *J*-Value (Hz)
2×OCH_2CH_3	1.20-1.30	m
CO_2CH_3	3.78	s
2×OCH_2CH_3	4.00-4.15	m
H-5"	6.84	app. t, 8.5
H-2" and *H*-6"	7.03	dd, 8.5 and 5.8
H-3'	7.18	d, 7.5
H-5'	7.44	t, 7.5
H-2 and *H*-4'	7.47-7.61	m
H-6'	7.98	d, 7.5

Table 3.15: Chemical shifts δ_C of the methyl ester **256**.

Assignment	Chemical Shift δ_C (ppm)	Multiplicity and *J*-Value (Hz)
2×OCH_2CH_3	15.79	d, 5.8
CO_2CH_3	51.57	s
OCH_2CH_3	61.65	d, 5.8
OCH_2CH_3	61.91	d, 6.8
C-3" and *C*-5"	114.88	d, 21.4
C-5'	127.59	d, 2.9
C-1	130.00	d, 185.6
C-6'	130.32	s
C-3'	130.39	d, 4.9
C-1"	130.64	dd, 23.3 and 2.9
C-1'	130.87	d, 3.9
C-2" and *C*-6"	131.39	d, 8.7
C-4'	131.94	d, 1.9
C-2'	135.85	d, 6.8
C-2	140.45	d, 9.7
C-4"	162.24	d, 250.7
CO_2H	166.91	s

3.6.5 Characterisation of diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-(*p*-methoxyphenyl)vinyl]phosphonate 242

In its first preparation, the acid **242** could not satisfactorily be separated from residual, hydrolysed starting material. A second attempt, however, yielded a solid that could easily be recrystallised from ethyl acetate/diethyl ether. In the proton NMR spectrum of analytically pure **242**, the phosphonate group is represented by two overlapping 3H-triplets at δ_H 1.16 and 1.17 ppm (CH_3) and a 4H-multiplet between δ_H 3.90 and 4.20 ppm (CH_2), respectively.

The protons of the methoxy moiety resonate at δ_H 3.69 ppm as a 3H-singlet, and the acidic proton appears as a broad singlet at δ_H 12.74 ppm. Two doublets are observed at δ_H 6.75 and 6.97 ppm, which are due to the protons of the methoxy-substituted benzene ring. The signals arising from the other phenyl protons are visible at δ_H 7.09 (*H*-3'), 7.48 (*H*-5'), 7.56 (*H*-4') and 7.95 (*H*-6') ppm. A doublet with $^3J_{P\text{-}H}$ 24.6 Hz is assigned to *H*-2. The multiplicities and coupling constants of the above-mentioned signals are listed in **Table 3.16**.

Table 3.16: Chemical shifts δ_H of the vinylphosphonate **242**.

Assignment	Chemical Shift δ_H (ppm)	Multiplicity and *J*-Value (Hz)
OCH_2CH_3	1.16	t, 7.0
OCH_2CH_3	1.17	t, 7.0
OCH_3	3.69	s
$2\times OCH_2CH_3$	3.90-4.20	m
H-3" and *H*-5"	6.75	d, 8.6
H-2" and *H*-6"	6.97	d, 9.0
H-3'	7.09	d, 8.0
H-2	7.31	d, 24.6
H-5'	7.48	t, 7.5
H-4'	7.56	t, 7.5
H-6'	7.95	d, 7.0
CO_2H	12.74	s

Assignment of the ^{13}C NMR spectrum was again assisted by DEPT and ^{13}C-^1H COSY experiments. Thus, a doublet with $^3J_{P\text{-}C}$ 5.8 at δ_C 16.12 ppm and two more doublets at δ_C 61.21 and 61.66 ppm were identified as signals due to the CH_2 and CH_3 carbons of the diethyl phosphonate group. The methyl ether group OCH_3 is represented by a singlet at δ_C 55.13 ppm, and the tertiary carbons of the phenyl ring, to which the methoxy group is attached, resonate at δ_C 113.78 (*C*-3" and *C*-5") and 131.42 (*C*-2"and *C*-6") ppm. A doublet, for which a coupling constant of 23.3 Hz is observed, appears at δ_C 127.33 ppm and is assigned to *C*-1".

Due to the oxygen of the methoxy moiety, the remaining carbon *C*-4" of this phenyl unit is found very far downfield at δ_C 159.66 ppm. Other important features of this spectrum are a singlet at δ_C 167.71 ppm corresponding to CO_2H, a doublet with $^1J_{P\text{-}C}$ 184.6 Hz at δ_C 128.65 ppm due to *C*-1, and another doublet at δ_C 140.13 ppm, which has a coupling constant of 10.7 Hz, arises from *C*-2. The chemical shifts δ_C of the remaining signals, together with their assignment and multiplicities, can be seen in **Table 3.17**.

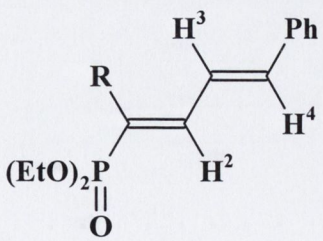
Table 3.17: Chemical shifts δ_C of the methoxy-derivative **242**.

Assignment	Chemical Shift δ_C (ppm)	Multiplicity and *J*-Value (Hz)
$2\times OCH_2CH_3$	16.12	d, 5.8
OCH_3	55.13	s
OCH_2CH_3	61.21	d, 4.9
OCH_2CH_3	61.66	d, 5.8
C-3" and *C*-5"	113.78	s
C-1"	127.33	d, 23.3
C-5'	127.95	s
C-1	128.65	d, 184.6
C-6'	130.47	s
C-3'	130.63	d, 5.8
C-2" and *C*-6"	131.42	s
C-1'	131.89	d, 3.9
C-4'	132.27	s
C-2'	136.75	d, 6.8
C-2	140.13	d, 10.7
C-4"	159.66	s
CO_2H	167.71	s

3.6.6 Characterisation of diethyl (1*E*,3*E*)-[1-(*o*-carboxyphenyl)-4-phenyl-buta-1,3-dienyl]phosphonate 254

Similarly to the preceding ^{1}H NMR spectra of the other vinylphosphonates, the proton NMR spectrum of diethyl (1*E*,3*E*)-[1-(*o*-carboxyphenyl)-4-phenylbuta-1,3-dienyl]phosphonate **254** shows two 3H-triplets (*J* 7.0 Hz), which are centred at δ_H 1.15 and 1.20 ppm for the methyl protons and a 4H-multiplet between δ_H 3.90 and 4.05 ppm for the methylene protons of the phosphonate group. A broad 1H-singlet at δ_H 12.78 ppm corresponds to the acid proton.

^{1}H-^{1}H COSY analysis confirmed that a 5H-multiplet in the range of δ_H 7.25-7.35 ppm corresponds to the five protons of the unsubstituted benzene ring. A doublet with *J* 7.5 Hz at δ_H 7.91 ppm arises from *H*-6', and the proton of *C*-4' is represented by a 1H-triplet at δ_H 7.61 ppm with a coupling constant of 7.5 Hz. A double triplet at δ_H 7.50 ppm (J_1 7.5, J_2 7.5 and J_3 1 Hz) is assigned to *H*-5'. One part of the 2H-multiplet at δ_H 7.12-7.24 ppm is due to *H*-3' as evidenced from the ^{1}H-^{1}H COSY spectrum. The other part of this signal is a double doublet with $^3J_{1,P\text{-}H}$ 21.6 Hz and J_2 11.0 Hz, which arises from the vinyl proton *H*-2. The butadienyl proton *H*-4 resonates as a doublet (*J* 15.6 Hz), which is centred at δ_H 7.08 ppm, and a doublet of a doublet of doublets at δ_H 6.41 ppm unambiguously represents *H*-3. In addition to the coupling constants of 11.0 and 15.6 Hz due to its neighbouring protons, long-range coupling ($^4J_{P\text{-}H}$ 2.5 Hz) between the proton attached to *C*-3 and phosphorus is also observed. From the *J*-values, 15.6 and 21.6 Hz, of the vinyl protons it can be rationalised that both double bonds of the novel phosphonate **254** must be (*E*)-configured. The assignments of *H*-2, *H*-3 and *H*-4 as well as the proposed geometry of the two double bonds of **254** also agree favourably with the data reported[123] for the butadiene **261** (**Table 3.18**).



254

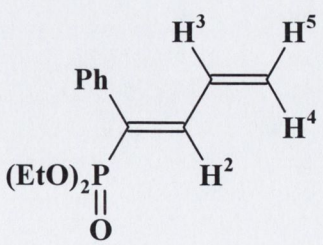


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Table 3.18: Comparison of the chemical shifts δ_H and the coupling constants of the butadienes **254** and **261**.

Butadiene **254**			Butadiene **261**	
δ_H (ppm)	multiplicity & *J*-values (Hz)	H^n	δ_H (ppm)	multiplicity & *J*-values (Hz)
7.18	dd, 21.6 and 11.0	n = 2	7.20	dd, 21.7 and 11.0
6.41	ddd, 15.6, 11.0 and 2.5	n = 3	6.33	ddd, 17, 11.0 and 10.1
7.08	d, 15.6	n = 4	5.68	d, 17.0
---	---	n = 5	5.43	d, 10.1

A ^{13}C-^{1}H COSY experiment was used to help to assign the signals in the carbon NMR spectrum of **254** (**Table 3.19**). A doublet ($^{3}J_{P\text{-}C}$ 5.8 Hz) due to the methyl group protons is evident at δ_C 16.13 ppm, and two more doublets with $^{2}J_{P\text{-}C}$ 5.8 Hz centred at δ_C 61.65 and 61.30 ppm, respectively, correspond to the methylene carbons of the phosphonate function. Another doublet ($^{1}J_{P\text{-}C}$ 186.6 Hz) at δ_C 131.05 ppm arises from *C*-1 of the butadiene moiety. The signal representing *C*-2 is centred at δ_C 141.39 ppm and has a coupling constant of 9.7 Hz, whereas the doublet at δ_C 123.79 ppm with $^{3}J_{P\text{-}C}$ 21.4 Hz is due to *C*-3. The last vinyl carbon *C*-4 resonates at δ_C 139.01 ppm. More information on the signals due to the remaining carbons of this compound **254** can be obtained from **Table 3.19**.

Table 3.19: Chemical shifts δ_C of the butadiene **254**.

Assignment	Chemical Shift δ_C (ppm)	Multiplicity and *J*-Value (Hz)
2×OCH_2CH_3	16.13	d, 5.8
OCH_2CH_3	61.30	d, 5.8
OCH_2CH_3	61.65	d, 5.8
C-3	123.79	d, 21.4
C-2" and *C*-6"	126.87	s
C-5'	127.98	s
C-3", *C*-4" and *C*-5"	128.87	s
C-6'	130.06	s
C-1	131.05	d, 186.6
C-3'	131.08	d, 4.9
C-4'	131.48	s
C-1'	132.23	d, 4.9
C-2'	135.30	d, 7.8
C-1"	135.91	s
C-4	139.01	s
C-2	141.39	d, 9.7
CO_2H	167.92	s

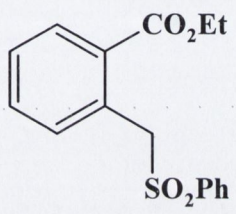
3.7 Conclusions and future work

A new reaction, which was initially uncovered recently by O'Neill,[60] between aldehydes and deprotonated diethyl (2-carboethoxy)benzylphosphonate **232** has been presented, its scope and limitations have been determined, and a mechanism for the new reaction has been proposed. The preparation of the starting materials is straightforward and involves mostly inexpensive reagents and facile work-up procedures, which also accounts for the novel reaction itself. The reaction conditions of the original procedure[60] have been improved and the novel vinylphosphonates **111**, **205**, **226**, **254**, **256** and **257** were obtained in moderate to excellent yields. With some aldehydes, namely 4-nitrobenzaldehyde **225**, trimethyl-acetaldehyde **250** and 2-formylpyrrole **252**, this new reaction did not proceed and the expected vinylphosphonates could not be isolated. In the case of trimethylacetaldehyde **250** this was probably due to the steric demands of the tertiary butyl group, which might have prevented the abstraction of the acidic proton of the proposed lactone intermediate **260**, and hence, the cleavage of the lactone ring. It was also shown that under the given conditions, ketones like acetophenone **258a** or cyclopentanone **258b** do not undergo Stobbe-like reactions to yield vinylphosphonates.

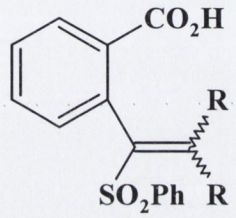
The products have been characterised by standard analytical procedures (NMR and IR spectroscopy, elemental analysis, etc.) and the geometry of the vinyl group has been clarified, *i.e.*, all of the vinylphosphonates have a *trans*-geometry relative to the phosphonate group. The geometry is an unexpected feature, and is probably due to the configuration of the preceding lactone intermediates. Future work might include further investigations on the effects of other solvents, and bases on the course of this reaction. Furthermore, it can be expected that also the size of the carboxyl ester group of the starting materials will have a strong influence on whether the Horner-Emmons olefins or the vinylphosphonates will be the predominant products, and phosphonates with bulkier carboalkoxy groups might be tested in this reaction. The same accounts for the phosphonate ester group of the starting material. Instead of ethyl esters, methyl, phenyl or otherwise-substituted phosphonates could be employed and the steric effects of these groups on the geometry of the products could be investigated.

Of course, one has to keep in mind the problem of transesterification that might occur if the carboxyl and phosphonate ester groups have different substituents. Finally, it would be desirable to use a wider range of chemically and sterically different aldehydes to explore the limitations of this facile new reaction.

With a number of novel vinylphosphonates successfully synthesised and analysed, it was decided to investigate Stobbe-like reactions between carbonyl compounds and reagents which are similar to the phosphonate **232**. The ethyl ester **126a** was considered as a potential molecule from which, *via* Stobbe-like reactions, the vinylsulfones **125a** might be obtained.



126a



125a

R = aryl, heteroaryl, styryl, *etc.*

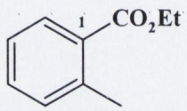
Thus, in **Chapter 4**, the objective was to prepare the phenyl sulfone **126a** and react its carbanion with aldehydes and ketones.

3.8 Experimental Section

General experimental conditions are the same as in **Chapter 2 (p80)**.

Ethyl *o*-toluate 248

To a flask containing *o*-toluic acid **122** (15.00 g; 0.11 mol), dissolved in ethanol (300 ml), was added concentrated sulfuric acid (15 ml). This mixture was heated at reflux for 6 h and was then cooled to room temperature. Ethanol was evaporated and the residual oil was redissolved in diethyl ether. The ethereal solution was washed with water, saturated sodium hydrogen carbonate solution and brine.

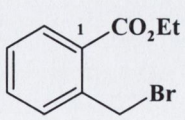


248

The organic layer was dried and the solvent was evaporated to give *ethyl o-toluate* **248** (12.80 g; 71 %) as a yellow oil that had, ν_{max} (L) 1720 cm^{-1}, δ_H 1.41 (3H, t, *J* 6.8, OCH_2CH_3), 2.63 (3H, s, Ph-CH_3), 4.38 (2H, q, *J* 6.8, OCH_2CH_3), 7.20-7.30 (2H, m, Ph*H*'s), 7.40 (1H, m, Ph*H*) and 7.94 (1H, d, *J* 8.0, Ph*H*) ppm.

Ethyl 2-(bromomethyl)benzoate 249[118a]

The ethyl ester **248** (15.00 g; 91 mmol) was dissolved in CCl_4 (250 ml) and to this was added *N*-bromosuccinimide (19.60 g; 0.11 mol) and a catalytic amount of AIBN (60 mg). After heating the mixture at reflux for 2.5 h, the contents of the flask were cooled, and solid succinimide was filtered off by suction filtration.

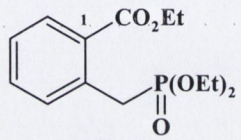


249

The filtrate was evaporated to give a yellow oil, which was distilled to yield *ethyl 2-(bromomethyl)benzoate* **249** as a colourless oil, b. p. 92-94 °C/0.1 mmHg, (*lit.*[118a] b. p. 100-105 °C/1.0 mmHg), ν_{max} (L) 1730 cm^{-1}, δ_H 1.44 (3H, t, *J* 7.3, $CO_2CH_2CH_3$), 4.43 (2H, q, *J* 7.3, $CO_2CH_2CH_3$), 4.98 (2H, s, CH_2Br), 7.38 (1H, m, *H*-5), 7.44-7.53 (2H, m, *H*-3 and *H*-4) and 7.98 (1H, d, *J* 7.5, *H*-6) ppm.

Diethyl (2-carboethoxy)benzylphosphonate 232[118b]

Ethyl 2-(bromomethyl)benzoate **249** (15.00 g; 62 mmol) and triethyl phosphite (11.00 g; 66 mmol) were heated at 160 °C for 24 h.



232

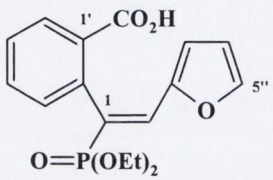
Distillation yielded *diethyl (2-carboethoxy)benzylphosphonate* **232** (13.60 g; 90 %) as a colourless oil, b. p. 138-140 °C/0.1 mmHg, (*lit.*[118b] b. p. 170-174 °C/0.1 mmHg), ν_{max} (L) 1718 and 1267 cm^{-1}, δ_H 1.21 (6H, t, *J* 7.2, OCH_2CH_3), 1.40 (3H, t, *J* 7.3, $CO_2CH_2CH_3$), 3.81 (2H, d, $^2J_{P-H}$ 23.2, PCH_2), 3.93-4.05 (4H, m, OCH_2CH_3), 4.32-4.40 (2H, q, *J* 7.2, $CO_2CH_2CH_3$), 7.31 (1H, m, Ph*H*), 7.35-7.48 (2H, m, Ph*H*'s) and 7.87 (1H, d, *J* 8.0, Ph*H*) ppm.

General procedure for reactions between diethyl (2-carboethoxy)benzylphosphonate 232 and an aldehyde

Diethyl (2-carboethoxy)benzylphosphonate **232** (1.20 g; 4 mmol) in dry DMF (5 mL) was added to ethanolic sodium ethoxide (1M; 12 mmol; 12 mL) at room temperature under nitrogen. After 5 min an aldehyde (4 mmol; neat or dissolved in a little DMF) was added and the mixture was stirred for 1 h. It was then diluted with water, and neutral products and residual starting materials were extracted using ether. The aqueous phase was then acidified to pH 1 using concentrated hydrochloric acid and extracted using ethyl acetate to give acidic products. Each of these

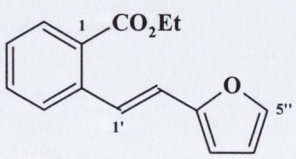
organic extracts was washed with brine, dried and evaporated. The crude neutral fraction was analysed by means of ^{1}H NMR spectroscopy. The acidic product generally solidified, and was further purified by recrystallisation from acetone, except where noted below.

Diethyl (*E*)-[1-*o*-carboxyphenyl-2-(2'-furyl)vinyl]phosphonate 111



111

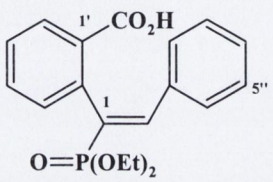
Following the general procedure, 2-furaldehyde **110** (0.38 g; 4 mmol) gave a crude acidic product that was recrystallised from acetone to afford *diethyl (E)-[1-o-carboxyphenyl-2-(2'-furyl)vinyl]phosphonate* **111** (0.89 g; 64 %) as a solid, m. p. 208-210 °C, ν_{max} (N) 2925, 2854, 1712, 1614, 1593, 1571, 1285, 1238, 1209, 1197, 1162, 1141, 1099, 1074, 1054, 1024, 977, 958, 932, 887, 876, 798, 760, 722 and 699 cm^{-1}, δ_H (DMSO-d_6) 1.15 (3H, t, *J* 7.0, OCH_2CH_3), 1.19 (3H, t, *J* 7.0, OCH_2CH_3), 3.90-4.05 (4H, m, OCH_2CH_3), 5.86 (1H, d, *J* 3.5, *H*-3" furyl), 6.40 (1H, dd, *J* 3.5 and 2.0, *H*-4" furyl), 7.18 (1H, d, $^{3}J_{P-H}$ 23.6, *H*-2), 7.18 (1H, d, *J* 7.5, *H*-3'), 7.50 (1H, t, *J* 7.8, *H*-5'), 7.55-7.67 (2H, m, *H*-4' aryl and *H*-5" furyl), 7.97 (1H, d, *J* 7.5, *H*-6') and 12.70 (1H, s, exch. D_2O, CO_2H) ppm, δ_C (100.6 MHz) 16.13 (d, $^{3}J_{P-C}$ 6.8, OCH_2CH_3), 61.41 (d, $^{2}J_{P-C}$ 5.8, OCH_2CH_3), 61.88 (d, $^{2}J_{P-C}$ 5.8, OCH_2CH_3), 112.13 (*C*-4"), 113.63 (*C*-3"), 127.98 (d, $^{1}J_{P-C}$ 187.6, *C*-1), 128.01 (*C*-5'), 128.29 (d, $^{2}J_{P-C}$ 11.7, *C*-2), 130.34 (d, $^{3}J_{P-C}$ 4.9, *C*-3'), 130.50 (*C*-6'), 131.00 (d, $^{3}J_{P-C}$ 4.9, *C*-1'), 132.13 (*C*-4'), 136.59 (d, $^{2}J_{P-C}$ 5.8, *C*-2'), 144.59 (*C*-5"), 150.62 (d, $^{3}J_{P-C}$ 27.2, *C*-2") and 167.37 (CO_2H) ppm, δ_P (162 MHz) 17.83 ppm, *calculated* for $C_{17}H_{19}O_6P$: C 58.27, H 5.47, *found* C 58.20, H 5.51 %.



112

Ethyl (E)-2-[2'-(2''-furyl)ethenyl]benzoate[60,61] **112** (0.10 g; 10 %) was obtained from the neutral extract as an oil, ν_{max} (L) 1720 cm^{-1}, δ_H 3.90 (3H, s, CO_2CH_3), 6.41 (2H, overlapping ms, *H*-3' and *H*-4'), 6.80 (1H, *J* 18.0, vinyl) and 7.20-7.90 (6H, m, vinyl *H* and Ar*H*'s) ppm.

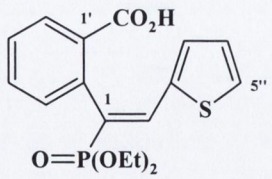
Diethyl (*E*)-[1-*o*-carboxyphenyl-2-phenylvinyl]phosphonate 205



205

Following the general procedure, benzaldehyde **170** (0.42 g; 4 mmol) gave a crude acidic product that was recrystallised from acetone to afford *diethyl (E)-[1-o-carboxyphenyl-2-phenylvinyl]phosphonate* **205** (1.29 g; 89 %) as a solid, m. p. 181-183 °C, ν_{max} (N) 2953, 2925, 2854, 1716, 1615, 1593, 1570, 1285, 1201, 1162, 1139, 1061, 1031, 985, 974, 873, 829, 800, 756, 721, 700 and 685 cm^{-1}, δ_H 1.16 (3H, t, *J* 7.0, OCH_2CH_3), 1.18 (3H, t, *J* 7.0, OCH_2CH_3), 3.98 (4H, apparent quintet, *J* 7.0, OCH_2CH_3), 7.00-7.13 (3H, m, *H*-3', *H*-2'' and *H*-6''), 7.15-7.25 (3H, m, *H*-3'', *H*-4'' and *H*-5''), 7.38 (1H, d, $^3J_{P-H}$ 24.6, *H*-2 vinyl), 7.48 (1H, t, *J* 7.5, *H*-5'), 7.54 (1H, t, *J* 7.0, *H*-4'), 7.95 (1H, d, *J* 7.5, *H*-6') and 12.80 (1H, s, exch. D_2O, CO_2H) ppm, δ_C (100.6 MHz) 16.11 (d, $^3J_{P-C}$ 5.8, OCH_2CH_3), 61.38 (d, $^2J_{P-C}$ 5.8, OCH_2CH_3), 61.83 (d, $^2J_{P-C}$ 5.8, OCH_2CH_3), 128.02 (*C*-5'), 128.28 (*C*-3'' and *C*-5''), 128.81 (*C*-4''), 129.69 (*C*-2'' and *C*-6''), 130.45 (*C*-3' and *C*-6'), 131.79 (d, $^3J_{P-C}$ 3.9, *C*-1'), 131.83 (d, $^1J_{P-C}$ 182.7, *C*-1), 132.25 (*C*-4'), 134.78 (d, $^3J_{P-C}$ 22.4, *C*-1''), 136.52 (d, $^2J_{P-C}$ 6.8, *C*-2'), 140.26 (d, $^2J_{P-C}$ 9.7, *C*-2) and 167.70 (CO_2H) ppm, δ_P (162 MHz) 17.90 ppm, *calculated* for $C_{20}H_{23}O_5P$: C 63.33, H 5.83, *found* C 63.12, H 5.90 %.

Diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-(2'-thienyl)vinyl]phosphonate 226

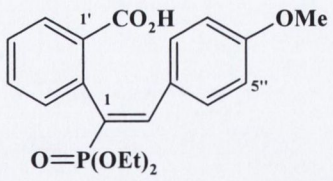


226

From thiophene-2-carboxaldehyde **220** (0.42 g; 4 mmol) there was obtained, after recrystallisation from acetone, diethyl *(E)-[1-(o-carboxyphenyl)-2-(2'-thienyl)-vinyl]phosphonate* **226** (1.02 g; 70 %) as a solid, m. p. 197-200 °C, ν_{max} (N) 2925, 2849, 2737, 2606, 1713, 1605, 1570, 1286, 1231, 1203, 1161, 1138, 1058, 1027, 976, 887, 853, 829, 801, 768, 742, 714, 673 and 631 cm^{-1}, δ_H 1.15 (3H, t, *J* 7.2, OCH_2CH_3), 1.19 (3H, t, *J* 7.5, OCH_2CH_3), 3.90-4.10 (4H, m, OCH_2CH_3), 6.99 (1H, apparent t, *J* 4.4, *H*-4" thienyl), 7.18 (1H, d, *J* 7.5, *H*-3'), 7.33 (1H, d, *J* 3.4, *H*-3" thienyl), 7.46 (1H, d, *J* 4.8, *H*-5" thienyl), 7.50-7.70 (3H, m, *H*-2, *H*-4' and *H*-5'), 8.01 (1H, d, *J* 7.5, *H*-6') and 12.71 (1H, s, exch. D_2O, CO_2H) ppm, δ_C (100.6 MHz) 16.14 (d, $^3J_{P\text{-}C}$ 5.8, OCH_2CH_3), 61.29 (d, $^2J_{P\text{-}C}$ 4.9, OCH_2CH_3), 61.79 (d, $^2J_{P\text{-}C}$ 5.8, OCH_2CH_3), 126.57 (*C*-4"), 127.76 (d, $^1J_{P\text{-}C}$ 188.0, *C*-1), 128.70 (*C*-5'), 130.55 (*C*-5"), 130.95 (*C*-6'), 131.29 (d, $^3J_{P\text{-}C}$ 4.9, *C*-3'), 131.71 (d, $^3J_{P\text{-}C}$ 4.9, *C*-1'), 132.63 (*C*-4'), 132.84 (*C*-3"), 134.07 (d, $^2J_{P\text{-}C}$ 12.6, *C*-2), 135.72 (d, $^2J_{P\text{-}C}$ 6.8, *C*-2'), 138.41 (d, $^3J_{P\text{-}C}$ 25.3, *C*-2") and 167.18 (CO_2H) ppm, δ_P (162 MHz) 18.08 ppm, *calculated* for $C_{17}H_{19}O_5PS$: C 55.74, H 5.19, *found* C 55.54, H 5.33 %.

Diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-(4-methoxyphenyl)vinyl]phosphonate 242 and diethyl (*E*)-[1-(*o*-carbomethoxyphenyl)-2-(4-methoxyphenyl)vinyl]phosphonate 257

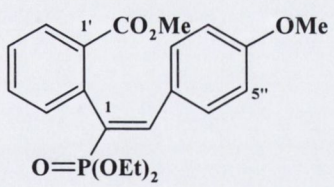
From 4-methoxybenzaldehyde **241** (0.54 g; 4 mmol) there was obtained *diethyl (E)-[1-(o-carboxyphenyl)-2-(4-methoxyphenyl)vinyl]phosphonate* **242** as a viscous *oil* (1.24 g; 79 %) that in the first preparation did not solidify, even after long periods of time, and was thus converted into the methyl ester **257**. From a second experiment, using the same amounts, the acid **242** was isolated as a white solid.



242

Recrystallisation of this from EtOAc/Et_2O afforded white crystals that had m. p. 118-120 °C, ν_{max} (N) 2953, 2924, 2854, 2612, 2504, 2367, 1711, 1616, 1605, 1571, 1510, 1459, 1419, 1377, 1300, 1254, 1190, 1178, 1128, 1098, 1052, 1024, 991, 975, 952, 898, 831, 798, 790, 769, 721 and 708 cm^{-1}, δ_H 1.16 (3H, t, *J* 7.0, OCH_2CH_3), 1.17 (3H, t, *J* 7.0, OCH_2CH_3), 3.69 (3H, s, OCH_3), 3.90-4.20 (4H, m, OCH_2CH_3), 6.75 (2H, d, *J* 8.6, *H*-3" and *H*-5"), 6.97 (2H, d, *J* 9.0, *H*-2" and *H*-6"), 7.09 (1H, d, *J* 8.0, *H*-3'), 7.31 (1H, d, $^3J_{P\text{-}H}$ 24.6, *H*-2), 7.48 (1H, t, *J* 7.5, *H*-5'), 7.56 (1H, t, *J* 7.5, *H*-4'), 7.95 (1H, d, *J* 7.0, *H*-6') and 12.74 (1H, s, exch. D_2O, CO_2H) ppm, δ_C (100.6 MHz) 16.12 (d, $^3J_{P\text{-}C}$ 5.8, CH_3), 55.13 (OCH_3), 61.21 (d, $^2J_{P\text{-}C}$ 4.9, CH_2), 61.66 (d, $^2J_{P\text{-}C}$ 5.8, CH_2), 113.78 (*C*-3" and *C*-5"), 127.33 (d, $^3J_{P\text{-}C}$ 23.3, *C*-1"), 127.95 (*C*-5'), 128.65 (d, $^1J_{P\text{-}C}$ 184.6, *C*-1), 130.47 (*C*-6'), 130.63 (d, $^3J_{P\text{-}C}$ 5.8, *C*-3'), 131.42 (*C*-2" and *C*-6"), 131.89 (d, $^3J_{P\text{-}C}$ 3.9, *C*-1'), 132.27 (*C*-4'), 136.75 (d, $^2J_{P\text{-}C}$ 6.8, *C*-2'), 140.13 (d, $^2J_{P\text{-}C}$ 10.7, *C*-2), 159.66 (*C*-4") and 167.71 (CO_2H) ppm, δ_P (162 MHz) 18.60 ppm.

A portion of the acid **242** (1.00 g) from the first preparation was dissolved in ethyl acetate and methylated using a slight excess of ethereal diazomethane.

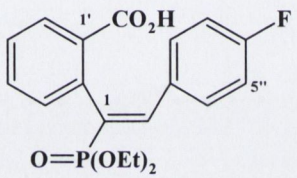


257

Column chromatography of the oily product afforded *diethyl (E)-[1-(o-carbomethoxyphenyl)-2-(4-methoxyphenyl)vinyl]phosphonate* **257** as a colourless oil (0.36 g) that had ν_{max} (L) 3462, 3064, 2983, 2953, 2906, 2839, 1726, 1604, 1572, 1512, 1481, 1460, 1444, 1390, 1367, 1294, 1254, 1180, 1130, 1082, 1051, 1026, 982, 964, 831, 779 and 712 cm^{-1}, δ_H 1.20-1.30 (6H, m, OCH_2CH_3), 3.74 (3H, s,

OCH_3), 3.77 (3H, s, CO_2CH_3), 4.00-4.15 (4H, m, OCH_2CH_3), 6.68 (2H, d, *J* 8.5, *H*-3" and *H*-5"), 6.98 (2H, d, *J* 8.5, *H*-2" and *H*-6"), 7.20 (1H, d, *J* 7.5, *H*-3'), 7.43 (1H, t, *J* 7.5, *H*-5'), 7.47-7.60 (2H, m, *H*-2 and *H*-4') and 7.98 (1H, d, *J* 7.5, *H*-6') ppm, δ_C (100.6 MHz): 15.79 (d, $^3J_{P\text{-}C}$ 6.8, OCH_2CH_3), 51.52 (CO_2CH_3), 54.71 (OCH_3), 61.51 (d, $^2J_{P\text{-}C}$ 5.8, OCH_2CH_3), 61.76 (d, $^2J_{P\text{-}C}$ 6.8, OCH_2CH_3), 113.24 (*C*-3" and *C*-5"), 127.12 (d, $^3J_{P\text{-}C}$ 23.3, *C*-1"), 127.28 (d, $^1J_{P\text{-}C}$ 186.6, *C*-1), 127.39 (*C*-5'), 130.32 (*C*-6'), 130.59 (d, $^4J_{P\text{-}C}$ 5.8, *C*-3'), 130.97 (d, $^3J_{P\text{-}C}$ 4.9, *C*-1'), 131.27 (*C*-2" and *C*-6"), 131.90 (*C*-4'), 136.37 (d, $^2J_{P\text{-}C}$ 7.8, *C*-2'), 141.47 (d, $^2J_{P\text{-}C}$ 10.7, *C*-2), 159.57 (*C*-4") and 167.08 (CO_2CH_3) ppm, δ_P (162 MHz) 19.03 ppm, HRMS (CI) *m/z* 393.1277: *calculated for* $[C_{20}H_{22}FO_5P+H]^+$ 393.1267.

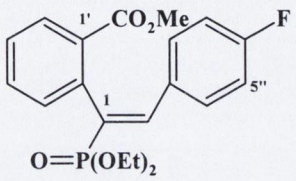
Diethyl (*E*)-[1-(*o*-carboxyphenyl)-2-(4-fluorophenyl)vinyl]phosphonate 230 and diethyl (*E*)-[1-(*o*-carbomethoxyphenyl)-2-(4-fluorophenyl)vinyl]phosphonate 256



230

From 4-fluorobenzaldehyde **224** (0.50 g; 4 mmol) there was obtained *diethyl (E)-[1-(o-carboxyphenyl)-2-(4-fluorophenyl)vinyl]phosphonate* **230** as a viscous oil (1.31 g; 87 %) that slowly became a solid that could not be recrystallised from any solvent. From a second experiment, using the exact same amounts, the acid **230** was isolated as white crystals. Recrystallisation of this from DCM afforded white crystals that had m. p. 176-178 °C, ν_{max} (N) 2953, 2924, 2854, 1711, 1615, 1593, 1569, 1460, 1377, 1201, 1162, 1139, 1060, 1030, 974, 874, 829, 799, 756, 721, 700, 685 and 632 cm^{-1}, δ_H 1.17 (3H, t, *J* 7.2, OCH_2CH_3), 1.31 (3H, t, *J* 7.2, OCH_2CH_3), 3.98-4.12 (2H, m, OCH_2CH_3), 4.16 (2H, apparent quintet, *J* 7.2, OCH_2CH_3), 6.82 (2H, apparent t, *J* 8.5, *H*-3" and *H*-5"), 7.00 (2H, dd, *J* 8.9 and 5.5, *H*-2" and *H*-6"), 7.13 (1H, d, *J* 7.5, *H*-3'), 7.43-7.55 (3H, m, *H*-2, *H*-4' and *H*-5') and 8.08 (1H, d, *J* 7.5, *H*-6') ppm, δ_C (100.6 MHz) 15.68 (d, $^3J_{P\text{-}C}$ 6.8, OCH_2CH_3), 15.78 (d, $^3J_{P\text{-}C}$ 6.8, OCH_2CH_3), 62.33 (d, $^2J_{P\text{-}C}$ 5.8, OCH_2CH_3), 62.69 (d, $^2J_{P\text{-}C}$ 5.8,

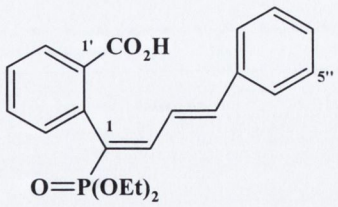
OCH_2CH_3), 114.95 (d, $^2J_{C\text{-}F}$ 22.2, *C*-3" and *C*-5"), 127.93 (d, $^5J_{P\text{-}C}$ 2.9, *C*-5'), 129.36 (d, $^1J_{P\text{-}C}$ 187.6, *C*-1), 130.06 (d, $^3J_{P\text{-}C}$ 4.9, *C*-3'), 130.34 (dd, $^3J_{P\text{-}C}$ 22.8 and $^4J_{C\text{-}F}$ 3.4, *C*-1"), 131.01 (*C*-6'), 131.50 (d, $^3J_{C\text{-}F}$ 8.7, *C*-2" and *C*-6"), C-1' probably obscured by *C*-2" and *C*-6", 132.15 (*C*-4'), 135.20 (d, $^2J_{P\text{-}C}$ 6.8, *C*-2'), 140.57 (d, $^2J_{P\text{-}C}$ 10.7, *C*-2), 162.34 (d, $^1J_{C\text{-}F}$ 250.7, *C*-4") and 169.29 (CO_2H) ppm, δ_P (162 MHz) 19.06, δ_F (376.4 MHz) –111.42 ppm.



256

A portion (0.74 g) of the oil which was obtained in the first preparation of **230** was dissolved in ethyl acetate and methylated using a slight excess of ethereal diazomethane. Column chromatography of the crude oily product afforded *diethyl (E)-[1-(o-carbomethoxyphenyl)-2-(4-fluorophenyl)vinyl]phosphonate* **256** as a colourless oil (0.45 g) that had ν_{max} (L) 3465, 3064, 2985, 2953, 2906, 1726, 1622, 1601, 1570, 1508, 1483, 1435, 1416, 1390, 1367, 1292, 1275, 1248, 1192, 1161, 1132, 1082, 1051, 1024, 984, 966, 837, 787, 729 and 714 cm^{-1}, δ_H 1.20-1.30 (6H, m, OCH_2CH_3), 3.78 (3H, s, CO_2CH_3), 4.00-4.15 (4H, m, OCH_2CH_3), 6.84 (2H, apparent t, *J* 8.5, *H*-3" and *H*-5"), 7.03 (2H, dd, *J* 8.5 and 5.8, *H*-2" and *H*-6"), 7.18 (1H, d, *J* 7.5, *H*-3'), 7.44 (1H, t, *J* 7.5, *H*-5'), 7.47-7.61 (2H, m, *H*-2 and *H*-4') and 7.98 (1H, d, *J* 7.5, *H*-6') ppm, δ_C (100.6 MHz) 15.79 (d, $^3J_{P\text{-}C}$ 5.8, OCH_2CH_3), 51.57 (CO_2CH_3), 61.65 (d, $^2J_{P\text{-}C}$ 5.8, OCH_2CH_3), 61.91 (d, $^2J_{P\text{-}C}$ 6.8, OCH_2CH_3), 114.88 (d, $^2J_{C\text{-}F}$ 21.4, *C*-3" and *C*-5"), 127.59 (d, $^5J_{P\text{-}C}$ 2.9, *C*-5'), 130.00 (d, $^1J_{P\text{-}C}$ 185.6, *C*-1), 130.32 (*C*-6'), 130.39 (d, $^3J_{P\text{-}C}$ 4.9, *C*-3'), 130.64 (dd, $^3J_{P\text{-}C}$ 23.3 and $^4J_{C\text{-}F}$ 2.9, *C*-1"), 130.87 (d, $^3J_{P\text{-}C}$ 3.9, *C*-1'), 131.39 (d, $^3J_{C\text{-}F}$ 8.7, *C*-2" and *C*-6"), 131.94 (d, $^4J_{P\text{-}C}$ 1.9, *C*-4'), 135.85 (d, $^2J_{P\text{-}C}$ 6.8, *C*-2'), 140.45 (d, $^2J_{P\text{-}C}$ 9.7, *C*-2), 162.24 (d, $^1J_{C\text{-}F}$ 250.7, *C*-4") and 166.91 (CO_2Me) ppm, δ_P (162 MHz) 18.20 ppm, δ_F (376.4 MHz) –111.83 ppm, HRMS (CI): *found m/z* 393.1277: *calculated for* $[C_{20}H_{22}FO_5P+H]^+$ 393.1267.

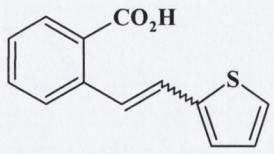
Diethyl (*E,E*)-[1-(*o*-carboxyphenyl)-4-phenylbuta-1,3-dienyl]phosphonate 254



254

From cinnamaldehyde **251** (0.53 g; 4 mmol) there was obtained after recrystallisation from acetone *diethyl (E,E)-[1-o-carboxyphenyl-4-phenylbuta-1,3-dienyl]phosphonate* **254** (0.82 g; 53 %) as a solid, m. p. 184-186 °C, ν_{max} (N) 2953, 2925, 2854, 1718, 1620, 1561, 1284, 1207, 1163, 1139, 1061, 1035, 974, 887, 795, 750, 722 and 690 cm^{-1}, δ_H 1.15 (3H, t, *J* 7.0, OCH_2CH_3), 1.20 (3H, t, *J* 7.0, OCH_2CH_3), 3.90-4.05 (4H, m, OCH_2CH_3), 6.41 (1H, ddd, *J* 15.6, 11.0 and 2.5, *H*-3), 7.08 (1H, d, *J* 15.6, *H*-4), 7.12-7.24 (2H, m, *H*-2 and *H*-3'), 7.25-7.35 (5H, m, *H*-2", *H*-3", *H*-4", *H*-5" and *H*-6"), 7.50 (1H, dt, *J* 7.5, 7.5 and 1.0, *H*-5'), 7.61 (1H, t, *J* 7.5, *H*-4'), 7.91 (1H, d, *J* 7.5, *H*-6') and 12.78 (1H, s, exch. D_2O, CO_2H) ppm, δ_C (100.6 MHz) 16.13 (d, $^3J_{P\text{-}C}$ 5.8, OCH_2CH_3), 61.30 (d, $^2J_{P\text{-}C}$ 5.8, OCH_2CH_3), 61.65 (d, $^2J_{P\text{-}C}$ 5.8, OCH_2CH_3), 123.79 (d, $^3J_{P\text{-}C}$ 21.4, *C*-3), 126.87 (*C*-2" and *C*-6"), 127.98 (*C*-5'), 128.87 (*C*-3", *C*-4" and *C*-5"), 130.06 (*C*-6'), 131.05 (d, $^1J_{P\text{-}C}$ 186.6, *C*-1), 131.08 (d, $^3J_{P\text{-}C}$ 4.9, *C*-3'), 131.48 (*C*-4'), 132.23 (d, $^3J_{P\text{-}C}$ 4.9, *C*-1'), 135.30 (d, $^2J_{P\text{-}C}$ 7.8, *C*-2'), 135.91 (*C*-1"), 139.01 (*C*-4), 141.39 (d, $^2J_{P\text{-}C}$ 9.7, *C*-2), 167.92 (CO_2H) ppm, δ_P (162 MHz) 17.93 ppm, *calculated* for $C_{20}H_{23}O_5P$: C 64.17, H 6.15, *found* C 64.19, H 6.11 %.

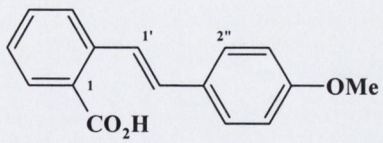
Murty reaction[115]



233

A 100 mL one-necked flask was charged with diethyl (2-carboethoxy)benzylphosphonate **232** (0.91 g; 3 mmol), dissolved in freshly distilled THF (20 mL). Finely ground KOH pellets (0.34 g; 6.1 mmol) were added and the mixture was stirred for 5 min. Thiophene-2-carboxaldehyde **220** (0.34 g; 3 mmol), dissolved in a little THF, was added and stirring was continued for 15 min, after which the mixture was filtered. The filtrate was acidified with diluted HCl and quickly extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated to give 0.81 g of a yellow oil. The ^{1}H NMR spectrum of the crude product mixture showed mostly unreacted starting material (phosphonate, aldehyde) and small amounts (~12 %) of the intended olefin **233**, which was not isolated.

Reaction between diethyl (2-carbomethoxy)benzylphosphonate 109 and 4-methoxybenzaldehyde 241: 2-[(*E*)-2-(4-methoxyphenyl)vinyl]benzoic acid 244[116]



244

A methanolic sodium methoxide solution (1M; 12 mmol; 12 mL) was prepared, then the solvent was evaporated. Crude diethyl (2-carbomethoxy)benzylphosphonate **109** (1.50 g; ~4 mmol) in dry DMF (15 mL) was added to the base while the mixture was stirred under an N_2-atmosphere and cooled in an ice-bath. After

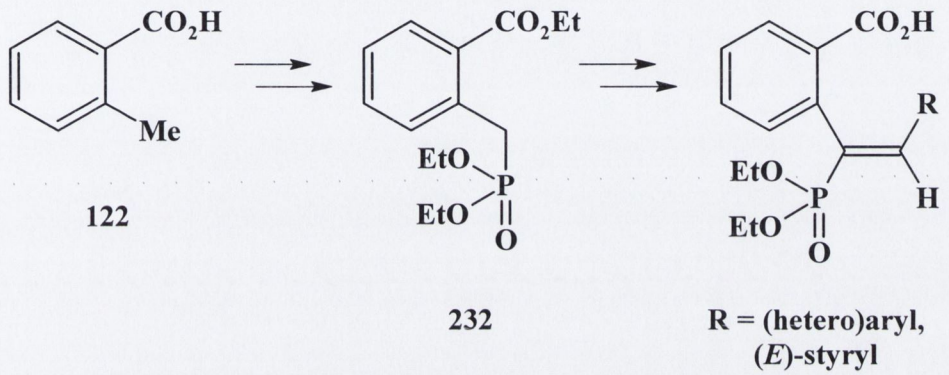
5 min 4-methoxybenzaldehyde **241** (0.49 mL; 4 mmol) was added and the mixture was stirred for 2 h. It was then diluted with water (50 mL) and extracted using diethyl ether. The aqueous phase was then acidified to pH 1 using concentrated hydrochloric acid and extracted with ethyl acetate. Both organic extracts were washed with brine, dried and the solvents evaporated *in vacuo*. The crude neutral fraction (0.25 g) was not further purified but analysed by means of ^{1}H NMR spectroscopy. The spectrum showed the presence of a mixture of compounds, one of which was the aldehyde **241**. Upon evaporation of the solvent the ethyl acetate extracts yielded a residue, which was chromatographed (SiO_2/ethyl acetate/hexane) to give a solid, which was recrystallised from diethyl ether. This procedure afforded pure *2-[(E)-2-(4-methoxyphenyl)vinyl]benzoic acid* **244** (0.30 g; 30 %) as a solid, (no m. p. obtained), ν_{max} (N) 2953, 2926, 2856, 1689, 1626, 1606, 1560, 1512, 1462, 1406, 1377, 1344, 1302, 1277, 1248, 1174, 1109, 1028, 966, 903, 823, 814, 800, 748, 715, 690 and 665 cm^{-1}, δ_H (DMSO-d_6) 3.78 (3H, s, OCH_3), 6.97 (2H, d, *J* 8.9, 2 × PhC*H*), 7.13 (1H, d, *J* 16.4, vinyl *H*), 7.35 (1H, t, *J* 7.5, *H*-5), 7.50 (1H, d, *J* 8.9, 2 × PhC*H*), 7.55 (1H, t, *J* 7.5, *H*-4), 7.75-7.87 (3H, m, vinyl *H*, *H*-3 and *H*-6) and 13.03 (1H, s, exch. D_2O, CO_2H) ppm.

CHAPTER 4:

Synthesis of novel vinylsulfones *via* Stobbe-like reactions

4.1 Introduction

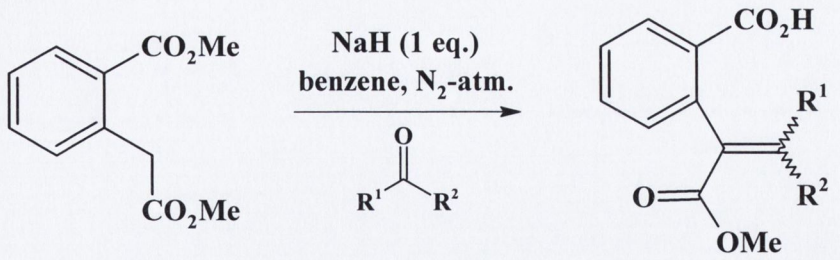
In **Chapter 3**, a successful and efficient route towards novel α,β-substituted vinylphosphonates has been established. From an inexpensive starting material, *i.e.* *o*-toluic acid **122**, the phosphonate **232** was obtained in three steps in a good overall yield. A Stobbe-like[59] reaction of the carbanion of **232** under Horner-Emmons reaction conditions then afforded the target compounds in moderate to very good yields and with excellent stereoselectivity (**Scheme 4.1**).



Scheme 4.1: Synthetic route towards the novel vinylphosphonates.

Naturally, the question was raised if analogous vinyl derivatives bearing other electron-withdrawing groups can be accessed *via* Stobbe-like reactions. Thus, a search in the literature was conducted to find reactions that employed benzoates that incorporate electron-withdrawing groups on a benzylic methylene group, which must be *ortho* to the ester function.

As has been mentioned in the introduction in **Section 1.10 (p45)**, Loewenthal and Pappo[62a] have reported on the synthesis of vinylcarboxylates **124a-d** (**Scheme 4.2**), which were derived from methyl 2-carbomethoxymethylbenzoate **123a**, the carbomethoxy ester analogue of the phosphonate **232**. This reaction was not only successful with benzaldehyde **170**, but also with acetone **258c**, cyclohexanone **258d** and benzophenone **200**.

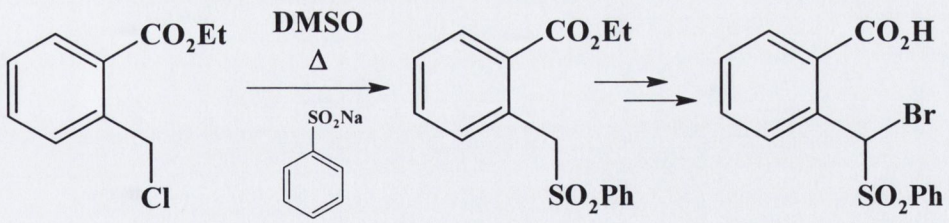


123a	**170**	$R^1 = Ph, R^2 = H$	**124a**	$R^1 = Ph, R^2 = H$
	258c	$R^1 = R^2 = Me$	**124b**	$R^1 = R^2 = Me$
	258d	$R^1, R^2 = -(CH_2)_5-$	**124c**	$R^1, R^2 = -(CH_2)_5-$
	200	$R^1 = R^2 = Ph$	**124d**	$R^1 = R^2 = Ph$

Scheme 4.2: Synthesis of vinylcarboxylates **124a-d** *via* Stobbe-like reactions.

The authors cited above did not provide any information on the geometry of the product **124a**. However, after a failed intramolecular cyclisation of **124a**, it was suggested[62a] that the *beta*-phenyl and the carbomethoxy group might have a *trans*-relationship, which might have prevented lactonisation of **124a**. The same compound **124a** was obtained from a similar reaction carried out by Cherney *et al.*,[62b] who also did not comment on the geometry of the vinyl group of this product.

The phenyl sulfone **126a** was considered another interesting candidate to be employed in Stobbe-like reactions. In 1973, Jarvis and Saukaitis[124] synthesised compound **126a** from ethyl 2-chloromethylbenzoate **262** and sodium benzene-sulfinate **263**, and then further reacted it to obtain the α-bromomethyl phenyl-sulfone **264** (**Scheme 4.3**).

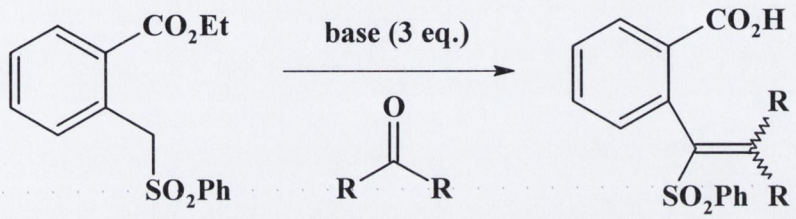


262 **263** **126a** **264**

Scheme 4.3: Synthesis of the phenyl sulfone **126a** from the benzyl chloride **262**.

4.2 Objectives

To the best of this author's knowledge, no Stobbe-like reactions have been attempted with compound **126a** before, its facile and inexpensive preparation made the phenyl sulfone **126a** an even more attractive starting point from which α,β-substituted vinylsulfones **125a** might be accessed. Thus, it was decided to investigate the reactions between the anion of **126a** and a selection of aliphatic and (hetero)aromatic aldehydes and ketones, respectively, according to **Scheme 4.4**.



126a **125a**

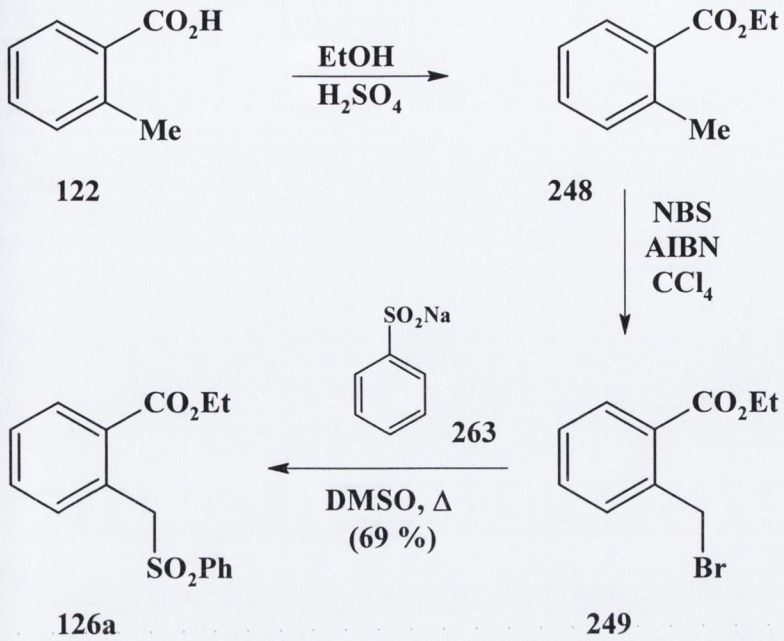
R = H, alkyl, (hetero)aryl, substituted aryl

Scheme 4.4: Synthetic strategy to obtain vinylsulfones **125a** *via* Stobbe-like reactions.

Initially, the strategy was to conduct the reactions shown in **Scheme 4.4** under the same conditions that were used in the synthesis of vinylphosphonates in **Chapter 3 (p125)**, and then, if necessary, modify and optimise the reaction parameters.

4.3 Synthetic route towards ethyl 2-[(phenylsulfonyl)methyl]benzoate 126a

The ethyl ester **126a** was obtained in a three-step synthesis (**Scheme 4.5**), of which the first two steps have already been described in the synthetic route towards the diethyl phosphonate **232** in **Chapter 3 (p125)**. Esterification of *o*-toluic acid **122** with ethanol and concentrated sulfuric acid yielded ethyl *o*-toluate **248**, and this was converted into the benzyl bromide **249** by means of NBS and AIBN as the radical initiator. In the final step, the bromide **249** was reacted with sodium benzenesulfinate **263** in DMSO solution to give the target compound **126a**.



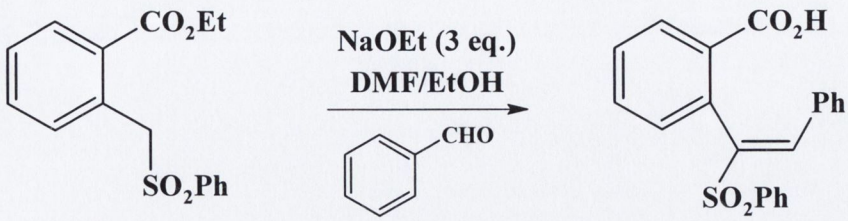
Scheme 4.5: Synthetic route towards the phenyl sulfone **126a**.

The last reaction in **Scheme 4.5** produced the desired ethyl ester **126a** in 69 % of the theoretical yield. An analytically pure sample of **126a** was characterised by the usual spectroscopic methods, and the data obtained from this perfectly matched the data reported by Jarvis and Saukaitis.[124] For example, the IR spectrum of **126a** showed an absorption at 1712 cm^{-1} corresponding to $\nu_{C=O}$ of the conjugated ester function. The two groups of signals between 1080 and 1170 cm^{-1} and between 1320 and 1300 cm^{-1}, respectively, are due to symmetrical and asymmetrical stretches of the SO_2-bonds. A key feature in the ^1H NMR spectrum of **126a** is a 2H-singlet at δ_H 5.09 ppm due to the methylene group, which is attached to the SO_2-function.

4.4 Stobbe-like reaction between the phenyl sulfone 126a and benzaldehyde 170

Similarly to the synthetic method used in the preparation of the vinylphosphonates, the sulfone **126a** was deprotonated with sodium ethoxide in ethanol and DMF solution and to this, benzaldehyde **170** was added (**Scheme 4.6**). The reaction was quenched with water and the mixture was extracted with ether. Evaporation of this

extract afforded some unchanged starting material, *i.e.*, the sulfone **126a**. When the aqueous layer was acidified with hydrochloric acid and then extracted with ethyl acetate, a white solid was obtained, which was identified as the novel vinylsulfone **265** by NMR spectroscopy.



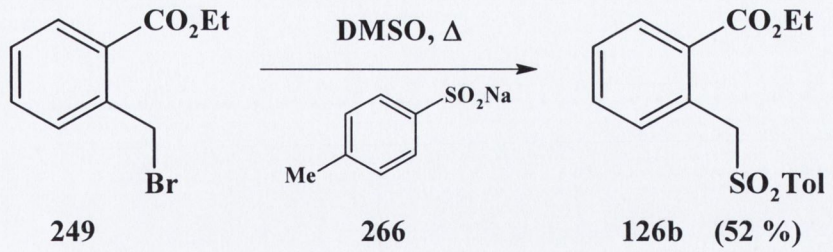
126a **170** **265 (92 %)**

Scheme 4.6: Reaction between deprotonated **126a** and benzaldehyde **170**.

A characteristic feature in the proton NMR spectrum of the unsaturated sulfone **265** is a 1H-singlet at δ_H 7.98 ppm, which represents the vinyl proton. The correlation between the chemical shift δ_H of this proton and the geometry of the double bond, together with all the other NMR data of this and the following novel vinylsulfones, will be discussed in **Section 4.8.4 (p177)**. The reaction shown above yielded 92 % of the desired product **265**, and most of the unreacted **126a** was recovered from the neutral extract in good purity. No additional by-products were observed.

4.5 Synthesis of a new sulfone reagent

Although the experiment described in the preceding Section had proved successful, it was decided to prepare a new starting material, which would facilitate the analysis of the products obtained from Stobbe-like reactions, especially the assignment of signals in the NMR spectra. It was thought that this might be achieved by replacing the phenyl sulfone group of compound **126a** with a tosyl moiety. Therefore, in another reaction the crude benzyl bromide **249** was dissolved in DMSO and heated with sodium *p*-tolylsulfinate **266** instead of the phenyl derivative **263**. From this reaction (**Scheme 4.7**), the *p*-tolyl sulfone **126b** was obtained in 52 % of the theoretical yield after recrystallisation.

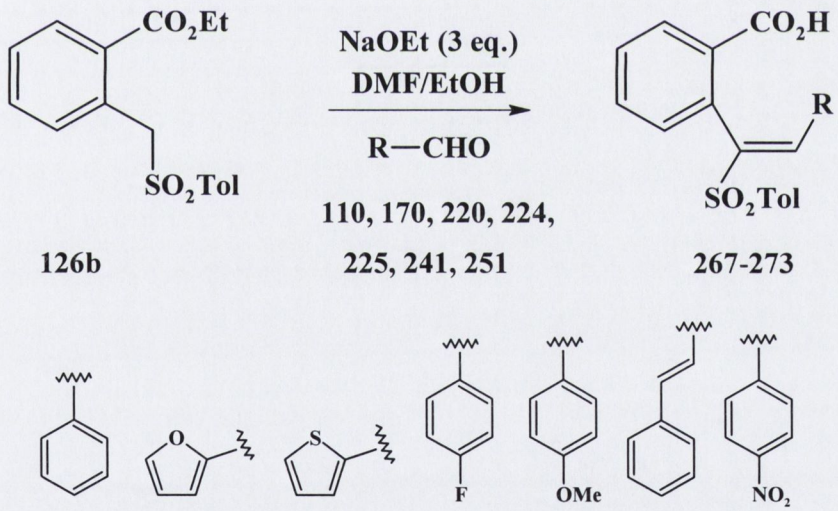


249 **266** **126b (52 %)**

Scheme 4.7: Preparation of the *p*-tolyl sulfone **126b** from the benzyl bromide **249**.

4.6 Stobbe-like reactions between the tolyl sulfone 126b and aldehydes

Like its benzene analogue **126a**, the *p*-tolyl sulfone **126b** is a known compound. It has been prepared by, *e.g.* Wildeman and co-workers,[125] who reported analytical data for **126b**, which closely matched the data obtained from the product of the present reaction. The new starting material was then employed in a series of reactions (**Scheme 4.8**), which were expected to produce the desired tosyl-substituted alkenes.



126b **110, 170, 220, 224, 225, 241, 251** **267-273**

Aldehyde:	**170**	**110**	**220**	**224**	**241**	**251**	**225**
Product:	**267**	**268**	**269**	**270**	**271**	**272**	**273**

Scheme 4.8: Stobbe-like reactions of the deprotonated *p*-tolyl sulfone **126b** with aldehydes.

The aldehydes that were employed in this reaction had already been used in the preparation of the vinylphosphonates in **Chapter 3**. This selection of reactants included benzaldehyde **170**, 2-furaldehyde **110**, thiophene-2-carboxaldehyde **220**, *p*-fluorobenzaldehyde **224**, *p*-methoxybenzaldehyde **241**, (*E*)-cinnamaldehyde **251** and *p*-nitrobenzaldehyde **225** (**Table 4.1**).

Table 4.1: Stobbe-like reactions between aldehydes and the anion of **126b**.

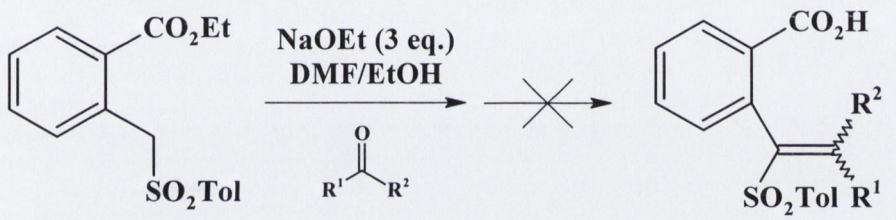
R	Aldehyde	Vinylsulfone	Yield (%)
Phenyl	**170**	**267**	92
2-Furyl	**110**	**268**	98
2-Thienyl	**220**	**269**	51
p-Fluorophenyl	**224**	**270**	79
p-Methoxyphenyl	**241**	**271**	73
(*E*)-2-Styryl	**251**	**272**	77
p-Nitrophenyl	**225**	**273**	0

As can be seen in **Table 4.1**, the vinylsulfones **267-272** were obtained in good to excellent yields, the exception being *p*-nitrophenylbenzaldehyde **225**, from which a yet unidentified compound was obtained, but no trace of the intended product **273** was observed. The yields of the unsaturated compounds **267-272** listed above represent the estimated amount of product, which was calculated from the integration values in the proton spectra of the crude products. Usually, the vinylsulfones were contaminated with small amounts of hydrolysed carboxyl ester **126b**, aldehydes that had been oxidised to their corresponding acids or residual DMF. These impurities sometimes impeded the recrystallisation of the products, which resulted in somewhat lower yields. Still, all vinylsulfones, except **273**, were isolated and fully characterised (*cf.* **Section 4.8, p171**). The ether extracts of the quenched vinylsulfone reaction mixtures were also analysed by ^{1}H NMR spectroscopy, and were found to contain solely unchanged tolyl sulfone **126b** and unreacted aldehyde, with one exception. Evaporation of the ether extracts obtained

from the reaction of 2-furaldehyde **110** afforded a brown oil, which consisted of a complex mixture of compounds. Separation of this mixture was not attempted as this fraction was very small. However, in the proton NMR spectrum two doublets with a coupling constant of 16.0 Hz are present, which is suggestive of an alkene with an (*E*)-configured double bond. This compound was most likely the "normal" Horner-Emmons product **112**.

4.7 Stobbe-like reactions between the tolyl sulfone 126b and ketones

After most of the reactions between the carbanion of **126b** and the aldehydes listed in **Table 4.1** had been successfully attempted, the next objective was to try to synthesise the vinylsulfones **274** and **275** from acetophenone **258a** and cyclohexanone **258d**, respectively (**Scheme 4.9**).



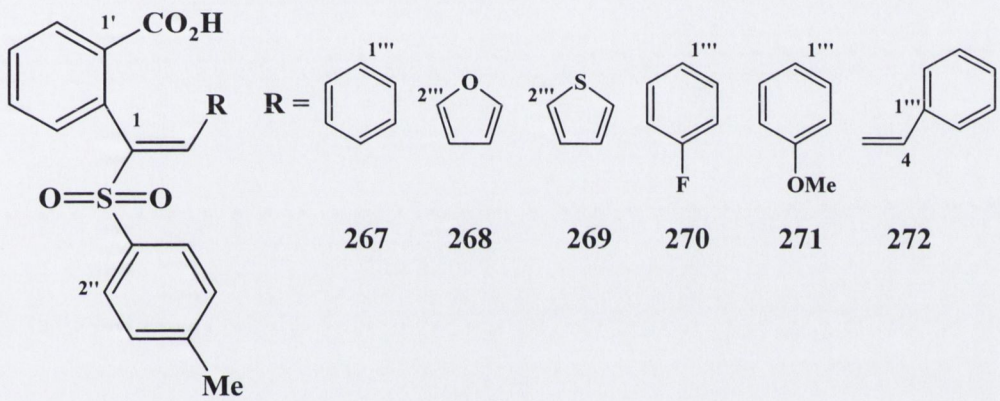
126b **258a** R^1 = Me, R^2 =Ph **274** R^1 = Me, R^2 =Ph
258d R^1, R^2 = -$(CH_2)_5$- **275** R^1, R^2 = -$(CH_2)_5$-

Scheme 4.9: Attempted Stobbe-like reactions employing acetophenone **258a** and cyclohexanone **258d**.

Three experiments were conducted in which acetophenone **258a** was added to deprotonated **126b**. On one occasion the mixture was stirred for one hour at room temperature. On another occasion, the reaction time was extended to 17 hours, and in a third reaction the solution was kept at 60 °C for 48 hours. In each case, there was obtained (hydrolysed) starting material only. Likewise, no vinylsulfone **275** could be isolated from the product mixture of cyclohexanone **258d** and the anion of **126b**, after these two reagents had been stirred for 14 hours at room temperature.

4.8 Characterisation of the vinylsulfones

The most characteristic absorptions in the infrared spectra of the novel vinylsulfones **267-272** are located between 1320 and 1300 cm^{-1} and between 1150 and 1140 cm^{-1}, which are frequency ranges where sulfones are expected[87] to absorb. Other significant features of these spectra are absorptions found within the ranges of 1700 and 1680 cm^{-1} and between 1640 and 1560 cm^{-1}, corresponding to conjugated carboxylic acid functions and aryl groups, respectively. The acids **267-272** were also analysed by HRMS and for each compound an *m/z*-signal was detected that matched the calculated $[M+Na]^+$ value (in case of the fluoro derivative: $[2M+Na]^+$). Further evidence for the successful synthesis of the alkenes **267-272** was obtained from elemental analyses. The NMR data of the sulfones **267**, **271** and **272** will be discussed in detail in the following Sections.



4.8.1 NMR data for 2-{(*E*)-1-[(4-methylphenyl)sulfonyl]-2-phenylvinyl}-benzoic acid 267

The ^1H NMR spectrum of the acid **267** (**Figure 4.1** and **Table 4.2**) was assigned as follows. For this and all the other novel compounds **268-272**, a 3H-singlet is observed at δ_H ~2.36 ppm, which corresponds to the methyl protons of the tosyl group. A 5H-multiplet appears at δ_H 7.04-7.12 ppm, which was resolved by ^1H-^1H-COSY analysis. From this experiment it was deduced that the aforementioned signal is due to *H*-3' of the carboxy-substituted ring, due to tolyl *H*-3'' and *H*-5'' and due to *H*-2''' and *H*-6''' of the unsubstituted phenyl group. A triplet at δ_H 7.20 ppm arises from *H*-3''' and *H*-5''' of the latter aromatic ring, and has a coupling constant of 7.5 Hz.

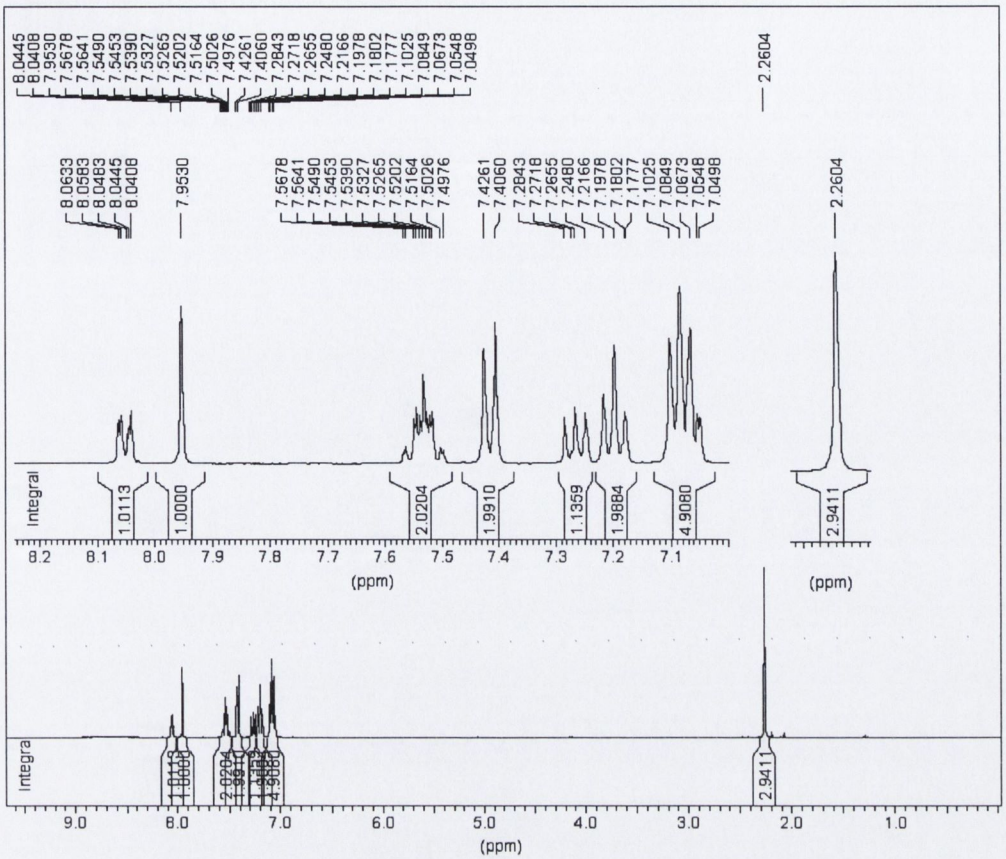


Figure 4.1: ^{1}H NMR spectrum of the vinylsulfone **267**.

Table 4.2: Chemical shifts δ_H of the phenyl-substituted vinylsulfone **267**.

Assignment	Chemical Shift δ_H (ppm)	Multiplicity and *J*-Value (Hz)
PhCH_3	2.26	s
H-3', *H*-3", *H*-5", *H*-2"' and *H*-6"'	7.04-7.12	m
H-3"' and *H*-5"'	7.20	t, 7.5
H-4"'	7.27	t, 7.3
H-2" and *H*-6"	7.42	d, 8.0
H-4' and *H*-5'	7.49-7.53	m
H-2	7.95	s
H-6'	8.05	m

The last proton of this group, *H*-4''', resonates at δ_H 7.27 ppm as a triplet with *J* 7.3 Hz. A 2H-doublet (*J* 8.0 Hz) centres at δ_H 7.42 ppm and is assigned to *H*-2'' and *H*-6''. The protons on *C*-4' and *C*-5' appear as a 2H-multiplet at δ_H 7.49-7.53 ppm, and *H*-6 resonates as a 1H-multiplet at δ_H 8.05 ppm. The remaining signal, a 1H-singlet at δ_H 7.95 ppm, must be due to the vinyl proton *H*-2.

In the ^{13}C NMR spectrum of **267** a signal at δ_C 21.05 ppm gives evidence for the methyl carbon, and a singlet at δ_C 170.40 ppm is unambiguously assigned to the carbon of the carboxylic acid function. The assignment of the other signals in this spectrum was assisted by DEPT, ^{13}C-^1H COSY and HMBC experiments and can be viewed in **Table 4.3**.

Table 4.3: Chemical shifts δ_C of the phenyl-substituted vinylsulfone **267**.

Assignment	Chemical Shift δ_H (ppm)	Assignment	Chemical Shift δ_H (ppm)
Ph-*C*H$_3$	21.05	*C*-2'	132.04
C-3''' and *C*-5'''	128.11	*C*-3'	132.59
C-2'' and *C*-6''	128.46	*C*-4'	132.68
C-3'' and *C*-5''	128.96	*C*-1'''	132.77
C-5'	129.06	*C*-1''	134.69
C-4'''	129.45	*C*-2	137.15
C-2''' and *C*-6'''	129.80	*C*-1	139.84
C-1'	130.53	*C*-4''	143.98
C-6'	130.97	*C*O$_2$H	170.40

4.8.2 NMR data for 2-{(*E*)-2-(4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonyl]vinyl}benzoic acid 271

The key features in the ^1H NMR spectrum of the alkene **271** (**Figure 4.2** and **Table 4.4**) are the acid proton at δ_H 12.79 ppm, a 3H-singlet at δ_H 3.69 ppm, which is due to the methoxy protons, and the vinyl proton resonating at δ_H 7.78 ppm.

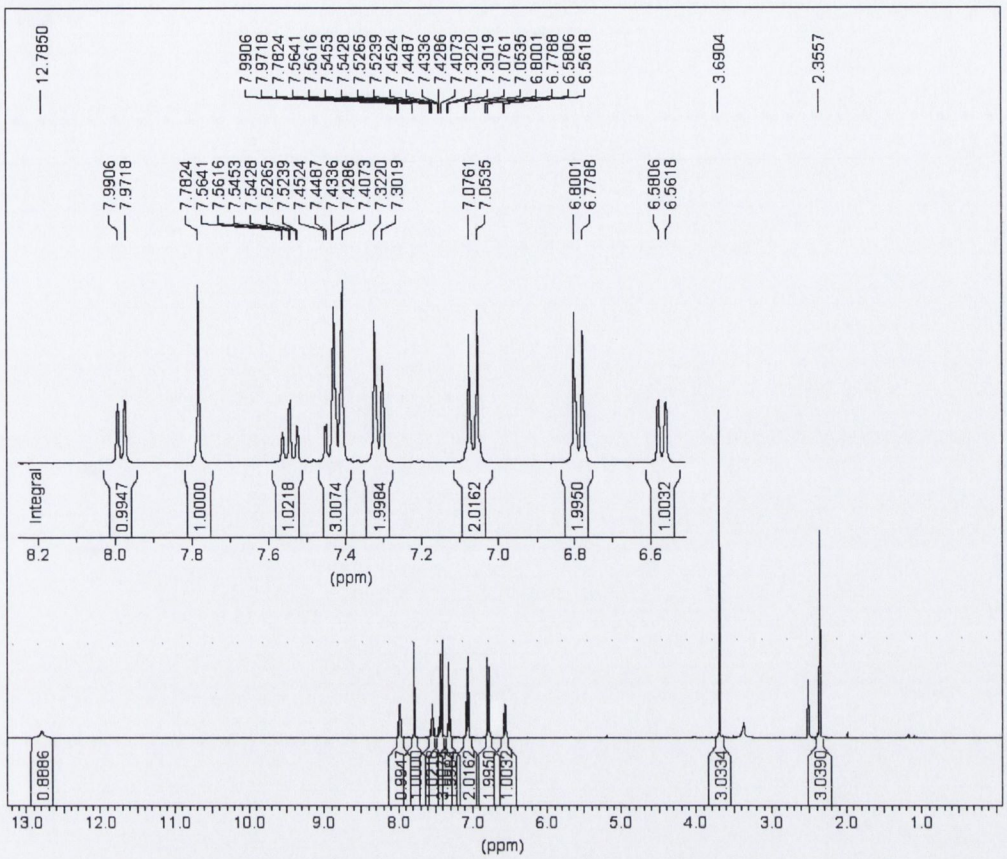


Figure 4.2: ^{1}H NMR spectrum of the *β*-(*p*-methoxyphenyl)vinylsulfone **271**.

Table 4.4: Chemical shifts δ_H of the vinylsulfone **271**.

Assignment	Chemical Shift δ_H (ppm)	Multiplicity and *J*-Value (Hz)
PhCH_3	2.36	s
PhOCH_3	3.69	m
H-3'	6.57	d, 7.5
H-3''', *H*-5'''	6.79	d, 8.5
H-2''' and *H*-6'''	7.06	d, 9.0
H-3'' and *H*-5''	7.31	d, 8.0
H-4', *H*-2'' and *H*-6''	7.39-7.47	m
H-5'	7.54	dt, 7.5, 7.5 and 1.0
H-2	7.78	s
H-6'	7.98	d, 7.5
CO_2H	12.79	s

Again, DEPT and ^{13}C-^{1}H COSY experiments helped to identify the signals in the ^{13}C NMR spectrum of **271**, and the chemical shifts δ_C of these resonances are shown in **Table 4.5**. The two most-upfield singlets are observed at δ_C 21.08 and 55.23 ppm and are assigned to the methyl carbons of the methoxy and the tolyl group, respectively. The carboxyl carbon is represented by a singlet at δ_C 167.08 ppm, and the tertiary carbons of the methoxy-substituted phenyl ring resonate at δ_C 114.07 ppm (*C*-3''' and *C*-5''') and at δ_C 131.92 ppm (*C*-2''' and *C*-6'''). These and all remaining signals are listed in **Table 4.5**.

Table 4.5: Chemical shifts δ_C of the methoxy derivative **271**.

Assignment	Chemical Shift δ_C (ppm)	Assignment	Chemical Shift δ_C (ppm)
Ph-*C*H$_3$	21.08	*C*-2''' and *C*-6'''	131.92
O*C*H$_3$	55.23	*C*-4'	132.14
C-3''' and *C*-5'''	114.07	Ph*C*	133.30
Ph*C*	125.50	Ph*C*	136.20
C-2'' and *C*-6''	128.02	*C*-2	136.53
C-5', *C*-3'' and *C*-5''	129.55	Ph*C*	138.33
C-6'	130.73	*C*-4''	143.82
Ph*C*	131.74	*C*-4'''	160.52
C-3'	131.88	*C*O$_2$H	167.08

4.8.3 NMR data for 2-{(1*E*,3*E*)-1-[(4-methylphenyl)sulfonyl]-4-phenylbuta-1,3-dien-1-yl}benzoic acid 272

In the ^{1}H NMR spectrum of **272** (**Figure 4.3** and **Table 4.6**), the signals due to the double bond protons of the butadiene resonate at δ_H 6.37, 7.05 and 7.69 ppm. The most-upfield resonance is a double doublet with *J* 15.6 and 11.0 Hz corresponding to *H*-3. The second signal appears as a doublet (*J* 15.5 Hz) and is assigned to *H*-4. A coupling constant of 11.6 Hz was calculated for the doublet which is due to *H*-2. The singlet at δ_H ~7.38 ppm arises from residual recrystallising solvent (benzene).

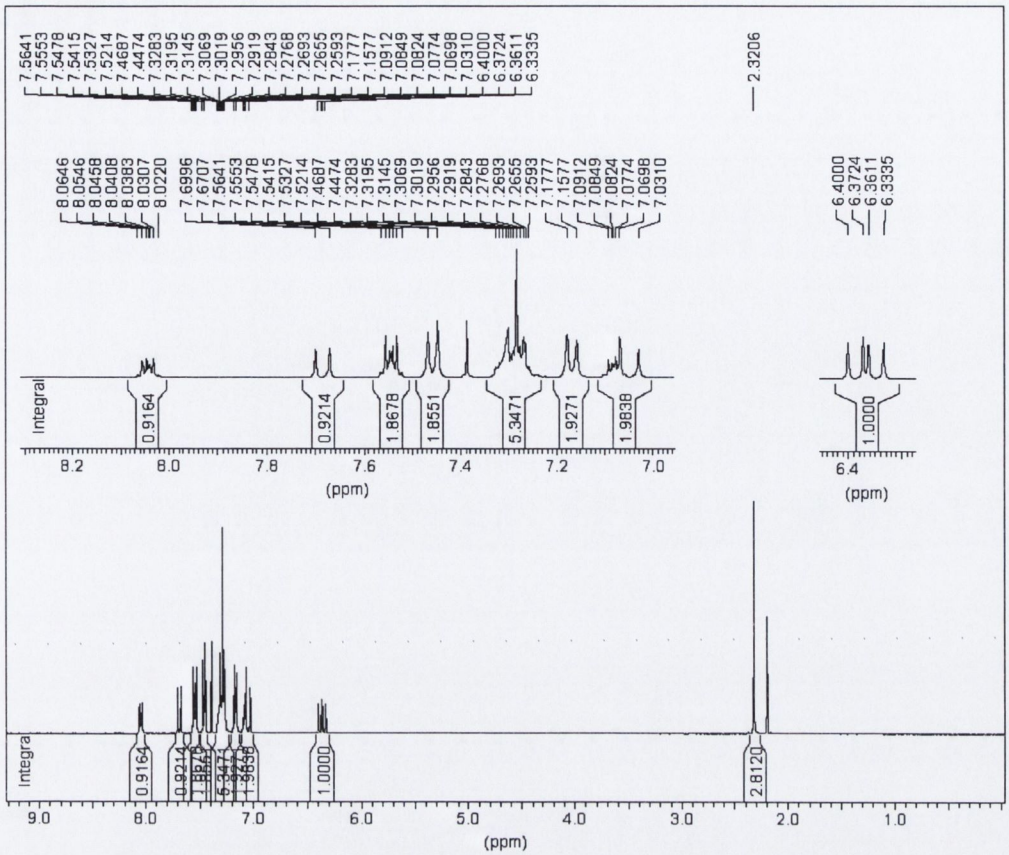


Figure 4.3: ^{1}H NMR spectrum of the butadiene **272**.

Table 4.6: Chemical shifts δ_H of the butadiene **272**.

Assignment	Chemical Shift δ_H (ppm)	Multiplicity and *J*-Value (Hz)
Ph-C*H*$_3$	2.32	s
H-3	6.37	dd, 15.6 and 11.0
H-4	7.05	d, 15.5
H-3'	7.09	m
H-3" and *H*-5"	7.17	d, 8.0
H-2"', *H*-3"', *H*-4"', *H*-5"' and *H*-6"'	7.25-7.35	m
H-2" and *H*-6"	7.46	d, 8.5
H-4' and *H*-5'	7.52-7.58	m
H-2	7.69	d, 11.6
H-6	8.04	m

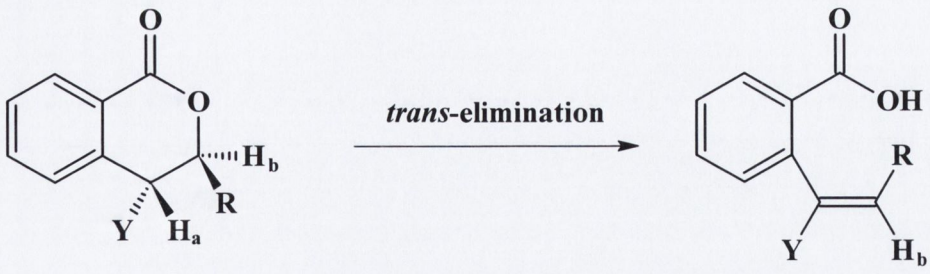
As can be seen from **Table 4.7**, the resonances due to the most significant carbons observed in the ^{13}C NMR spectrum of **272** could be assigned using ^{13}C-^{1}H COSY. Thus, a peak at δ_C 122.40 ppm was identified as *C*-3. A signal at δ_C 138.15 arises from *C*-2 and another one at δ_C 141.91 ppm corresponds to *C*-4. The primary carbon Ph-*C*H_3 and the quaternary carbon *C*O_2H are assigned to singlets at δ_C 21.08 and 169.42 ppm, respectively.

Table 4.7: Chemical shifts δ_C of the butadiene **272**.

Assignment	Chemical Shift δ_C (ppm)	Assignment	Chemical Shift δ_C (ppm)
Ph-*C*H_3	21.08	*C*-4'	131.89
C-3	122.40	*C*-3'	132.92
Ph*C*H	126.93	Ph*C*	135.32
Ph*C*H, *C*-2" and *C*-6"	128.24	Ph*C*	135.45
C-5'	128.81	*C*-2	138.15
Ph*C*H, *C*-3" and *C*-5"	128.98	Ph*C*	139.65
C-6'	130.72	*C*-4	141.91
Ph*C*	130.97	*C*-4"	143.84
Ph*C*	131.01	*C*O_2H	169.42

4.8.4 Geometry of the vinyl group of the novel sulfones 267-272

Assuming the formation of the vinylsulfones follows the same mechanistic pathways, which have been proposed for the novel vinylphosphonates presented in **Chapter 3**, both sets of compounds should have the same double bond configuration. As was discussed in **Section 3.6.1 (p131)**, the mechanism which leads to the novel phosphonates and sulfones, most probably proceeds *via* intermediate lactones that possess two asymmetric centres. The *trans*-compound **276** is considered the sterically most favourable isomer, which upon a concerted *trans*-elimination process (**Scheme 4.10**) might be converted into the (*E*)-configured alkene **277**.

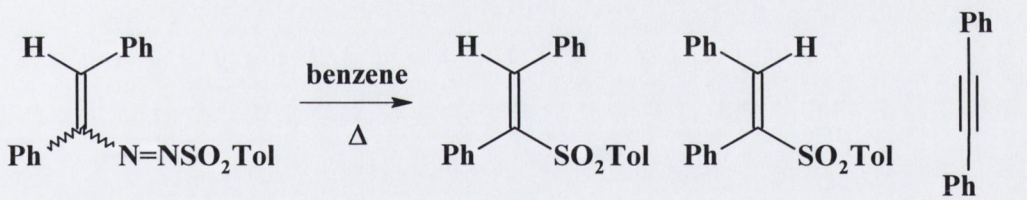


276 **277**

R = aryl, subst. aryl, *etc.* **Y = tosyl, diethoxyphosphoryl**

Scheme 4.10: *trans*-Elimination of the postulated intermediate lactone **276** to yield the vinylic products **277**.

Definite proof for the proposed double bond geometry assignments for the vinylphosphonate series (**Chapter 3**) was obtained from the ^{31}P-$^{1}H_b$ NMR coupling constants (*cf.* **Section 3.6.1, p131**). Of course, this NMR technique could not be applied to identify the alkene geometry of the vinylsulfones. Instead, it was thought that the ^{1}H NMR data of similar tri-substituted vinylsulfones[126-128] might support the proposed assignments shown above. In 1970, Rosini *et al.*[126] reported on the isolation of *p*-toluenesulfonyl-*trans*-stilbene **278** and the corresponding *cis*-isomer **279** from the decomposition of *p*-toluenesulfonylazostilbene **280** (**Scheme 4.11**).



280 **278** **279** **179c**

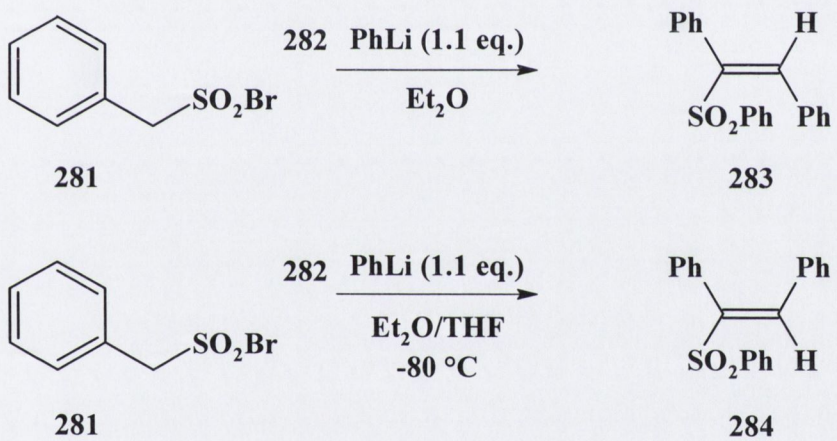
(34 %) **(34 %)** **(28 %)**

Scheme 4.11: Decomposition of *p*-toluenesulfonylazostilbene **280**.

The sulfones **278** and **279** were obtained in yields of 34 % each, and some diphenylacetylene **179c** (28 %) had also formed. The authors[126] then compared the analytical data, *i.e.*, melting points, IR and UV spectra, of the two stilbenes **278** and **279** with the data obtained from authentic samples of the same compounds prepared independently *via* a stereospecific route.[129]

Thus, the vinylsulfone **278** was assigned the (*Z*)-configuration and the stilbene **279** was assigned the (*E*)-configuration. In the proton NMR spectrum of the (*E*)-isomer **279**, the authors[126] identified a 1H-singlet at δ_H 8.20 ppm arising from the vinyl proton. The same proton of the (*Z*)-configured stilbene **278** resonated much further upfield, but was obscured by the signals due to the aromatic protons (δ_H 7.60-6.50 ppm).

Shirota, Nagai and Tokura[127] prepared sulfones which are very similar to the compounds **278** and **279**, respectively. From reactions between benzylsulfonyl-bromide **281** and phenyllithium **282** at ambient and at very low temperatures (**Scheme 4.12**), the authors isolated the isomeric vinylsulfones **283** and **284**, respectively, as minor by-products. The assignment of double bond geometry configuration of the two compounds **283** and **284**, however, was solely based on their melting points and UV spectra.



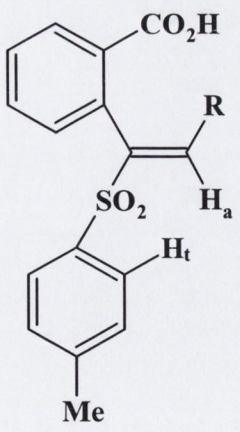
Scheme 4.12: Reaction between the sulfonylbromide **281** and phenyllithium **282**.

The lower melting solid, of which the vinyl proton resonated at δ_H 7.67 ppm in the NMR spectrum, was claimed to be the (*E*)-alkene **284**. The other compound was assigned as the (*Z*)-isomer **283** and had a vinyl proton, which appeared in the NMR spectrum as a singlet at δ_H 8.00 ppm. This is contradictory to the findings of Rosini and Ranza,[126] who had observed that the (*Z*)-stilbene **278** melts at a lower temperature than the (*E*)-isomer **279** and that its double bond proton resonates at a lower chemical shift in the NMR spectrum than the corresponding proton of the (*E*)-compound **279**.

A few years later Jarvis, Tong and Ammon[128] resolved this issue when they prepared the same sulfones **283** and **284** *via* stereospecific reactions,[129] and were able to show that the assignments made by Shirota *et al.*[127] must be wrong and should be reversed. This means that the vinyl protons of the (*Z*)-stilbenes **278** and **283**, respectively, resonate at chemical shifts of δ_H 7.70 ppm and lower, whereas the double bond protons of the corresponding (*E*)-isomers **279** and **284**, respectively, appear further downfield, *i.e.*, at δ_H ~8.00 ppm.

These values were compared with the chemical shifts of the vinyl protons H_a of the present unsaturated sulfones **267-272**. As can be seen in **Table 4.8**, each of the three alkenes **267**, **269** and **270** possesses a vinyl proton that resonates at *ca.* δ_H 8.00 ppm, which suggests the presence of an (*E*)-configured double bond. In the case of compounds **268**, **271** and **272**, the chemical shift of H_a is somewhat lower than δ_H 8.00 ppm. This is not unexpected, as the deshielding effects of the 2-furyl (**268**), *p*-methoxyphenyl (**271**) and (*E*)-styryl moiety (**272**) are weaker than that of the unsubstituted phenyl group (**267**). Of course, the effect of the *ortho*-benzoic acid group of the vinylsulfones **267-272** also has to be taken into account, and thus, no definitive statement about the vinyl group geometry of these alkenes can be made from these comparisons only.

Table 4.8: Chemical shifts of the vinyl protons H_a of the α,β-unsaturated vinylsulfones **267-272**.



R	Entry	δ_{Ha}
Phenyl	**267**	7.95
2-Furyl	**268**	7.64
2-Thienyl	**269**	8.07
p-Fluorophenyl	**270**	7.92
p-Methoxyphenyl	**271**	7.78
(*E*)-2-Styryl	**272**	7.69

More conclusive evidence for the proposed double bond geometry of the novel vinylsulfone **267** was obtained from the following NMR experiments. **Figure 4.4** shows a stacked plot of three spectra of the vinylsulfone **267**, the 'normal' proton spectrum and two n.O.e. experiments. In the first n.O.e. experiment, the NMR sample of **267** was exposed to a frequency corresponding to the singlet at δ_H 7.95 ppm, which is due to the vinyl proton H_a. As is shown in the second spectrum in **Figure 4.4**, this signal is coupling to two other resonances, a doublet at δ_H 7.09 ppm arising from the *ortho*-protons of the unsubstituted benzene ring and another doublet at δ_H 7.42 ppm due to the *ortho*-protons H_t of the tosyl group. Coupling between H_t and H_a is of course only possible, if the double bond possesses the (*E*)-configuration. In a control n.O.e. experiment (third spectrum in **Figure 4.4**), the frequency corresponding to the doublet at δ_H 7.42 ppm was used, and this caused the appearance of the two singlets due to the vinyl proton and the two *meta*-protons of the tosyl-function, respectively.

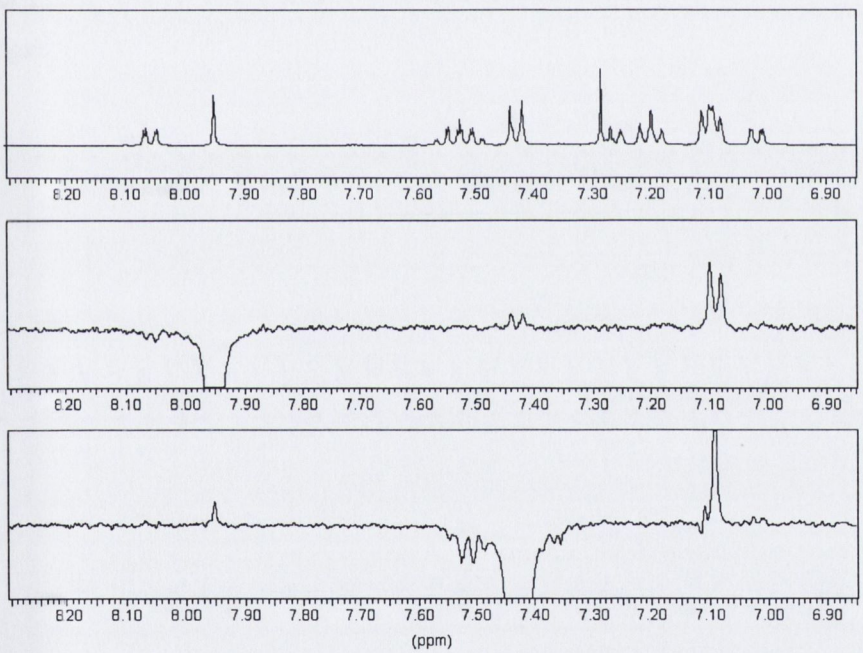


Figure 4.4: ^{1}H NMR spectrum and n.O.e. experiments of the vinylsulfone **267**.

The evidence obtained so far in order to characterise the novel compounds **267-272** was considered rather convincing. However, for absolute certainty it was decided to get an X-ray crystal structure of one of the vinylsulfones, and results of this analysis may be added later in an Appendix to this Thesis.

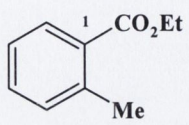
4.9 Conclusions and future work

As was shown in this Chapter, the vinylsulfones **267-272** can be synthesised *via* Stobbe-like reactions from the readily accessible benzylic sulfone **126b**, which in turn can be prepared from inexpensive starting materials. The novel compounds **267-272** were obtained in crude form in mediocre to excellent yields, but were sometimes a little difficult to purify. No vinylsulfone **273** was found from reaction of the carbanion of benzylic sulfone **126b** with *p*-nitrobenzaldehyde **225**, instead a red solid was obtained, which has not been identified yet. A *cis*-relationship between the sulfone group and the vinyl proton has been proposed for the sulfones **267-272**, and this geometry was confirmed by n.O.e. experiments. Unfortunately, acetophenone **258a** and cyclohexanone **258d** did not undergo Stobbe-like reactions with deprotonated **126b**, the sole products being (hydrolysed) starting materials. To find more suitable conditions for reactions involving ketones, as well as employing a wider range of aldehydes in this type of reaction, might be the subject of further investigations.

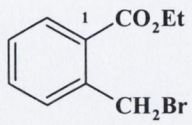
4.10 Experimental Section

General experimental conditions are the same as in **Chapter 2 (p80)**.

Ethyl *o*-toluate 248 and ethyl 2-(bromomethyl)benzoate 249



248

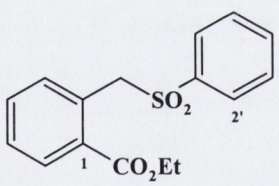


249

The ethyl ester **248** and the benzyl bromide **249** were prepared according to the same methods described in the Experimental Section of **Chapter 3 (p151)**.

Ethyl 2-[(phenylsulfonyl)methyl]benzoate 126a[124]

The sodium salt of benzenesulfinic acid monohydrate **263** (9.00 g; 49 mmol) was dissolved in DMSO (80 mL) and stirred at 60 °C. Crude ethyl 2-(bromomethyl)-benzoate **249** (11.70 g; 48 mmol) was added and stirring was continued at 60 °C for 2 h. The solution was diluted with water (350 mL) and extracted with dichloro-methane.



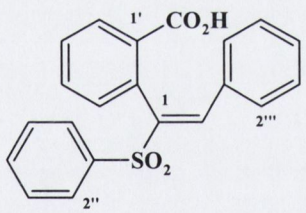
126a

Evaporation of the dried organic extracts yielded a white solid (14.06 g), which was recrystallised from dichloromethane/hexane to give pure *ethyl 2-[(phenylsulfonyl)-methyl]benzoate* **126a** (10.02 g; 69 %) as a solid that had m. p. 94-95 °C, (*lit.*[124] m. p. 91-92 °C), ν_{max} (N) 3010, 2926, 2858, 1712, 1601, 1581, 1448, 1408, 1377, 1296, 1271, 1198, 1163, 1144, 1120, 1111, 1080, 1030, 964, 901, 887, 791, 756, 712 and 688 cm^{-1}, δ_H 1.35 (3H, t, *J* 7.0, CH_2CH_3), 4.21 (2H, q, *J* 7.3, CH_2CH_3), 5.09

(2H, s, SO_2CH_2), 7.33 (1H, dd, *J* 7.5 and 1.0, *H*-3), 7.39-7.53 (4H, m, *H*-4, *H*-5, *H*-3' and *H*-5'), 7.57-7.68 (3H, m, *H*-2', *H*-4' and *H*-6') and 7.91 (1H, dd, *J* 7.5 and *J* 1.5, *H*-6) ppm, δ_C (100.6 MHz) 14.09 (CH_2CH_3), 59.16 (SO_2CH_2), 61.18 (CH_2CH_3), 128.61 (*C*-2' and *C*-6'), 128.77 (*C*-5, *C*-3' and *C*-5'), 129.04 (*C*-1), 130.93 (*C*-6), 131.09 (*C*-2), 131.94 (*C*-4), 133.40 (*C*-3), 133.48 (*C*-4'), 138.33 (*C*-1') and 166.67 (CO_2H) ppm.

Reaction between ethyl 2-[(phenylsulfonyl)methyl]benzoate 126a and benzaldehyde 170: 2-[(*E*)-2-phenyl-1-(phenylsulfonyl)vinyl]benzoic acid 265

Ethyl 2-[(phenylsulfonyl)methyl]benzoate **126a** (1.22 g; 4 mmol) in dry DMF (5 mL) was added to ethanolic sodium ethoxide (1M; 12 mmol; 12 mL) at room temperature. After 5 min benzaldehyde **170** (0.42 g; 4 mmol; dissolved in a little DMF) was added and the mixture was stirred for 1 h. It was then diluted with water and extracted using diethyl ether. The aqueous phase was then acidified to pH 1 using diluted hydrochloric acid and extracted using ethyl acetate to give acidic products. Each of these organic extracts was washed with brine, dried and evaporated.



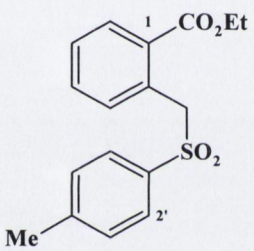
265

The ether layer produced an oily solid that contained solely starting materials (aldehyde **170** and sulfone **126a**), which was confirmed by ^{1}H NMR spectral analysis. Evaporation of the ethyl acetate extract afforded a white crystalline solid, which was recrystallised from DCM/hexane to afford *2-[(E)-2-phenyl-1-(phenylsulfonyl)vinyl]benzoic acid* **265** (1.34 g; 92 %) as fine, white crystals that had m. p. 199-201 °C, ν_{max} (N) 2952, 2923, 2853, 2649, 1697, 1630, 1595, 1571, 1459, 1400, 1377, 1303, 1265, 1144, 1082, 942, 922, 822, 806, 765, 755, 715, 684, 641 and 611 cm^{-1}, δ_H 7.01 (1H, dd, *J* 7.5 and 1.5, *H*-3'), 7.09 (2H, d, *J* 7.6, *H*-2''' and *H*-6'''), 7.20 (2H, t, *J* 7.3, *H*-3''' and *H*-5'''), 7.28 (1H, m, *H*-4'''), 7.33 (2H, t, *J* 7.8, *H*-3''

and *H*-5"), 7.43-7.60 (5H, m, *H*-4', *H*-5', *H*-2", *H*-4" and *H*-6"), 7.98 (1H, s, *H*-2) and 8.06 (1H, dd, *J* 7.8 and 1.7, *H*-6') ppm, δ_C (100.6 MHz) (one quaternary *C* is hidden) 128.12 (Ph*C*H), 128.36 (Ph*C*H), 128.39 (Ph*C*H), 129.11 (Ph*C*H), 129.55 (Ph*C*H), 129.83 (Ph*C*H), 130.56 (Ph*C*), 131.09 (Ph*C*H), 131.93 (Ph*C*), 132.48 (Ph*C*H), 132.66 (Ph*C*H), 132.98 (Ph*C*H), 137.57 (Ph*C*H), 137.80 (Ph*C*), 139.70 (Ph*C*) and 170.19 (*C*O_2H) ppm; HRMS (CI): *found m/z* 387.0679: *calculated for* $[C_{21}H_{16}SO_4+Na]^+$ 387.0667.

Ethyl 2-{[(4-methylphenyl)sulfonyl]methyl}benzoate 126b[125]

The sodium salt of toluene-4-sulfinic acid monohydrate **266** (33.00 g; 0.17 mol) was dissolved in DMSO (230 mL) at 50 °C. Crude ethyl 2-(bromomethyl)benzoate **249** (39.68 g; 0.16 mol) was added and the mixture was heated at 70 °C for 4 h. The solution was diluted with water (700 mL) and extracted with dichloromethane.



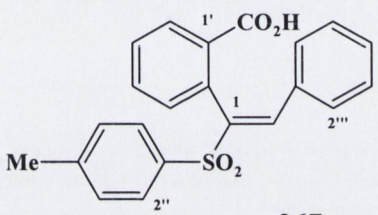
126b

Evaporation of the dried organic extracts yielded a white solid (29.93 g), which was recrystallised from diethyl ether/acetone to give pure *ethyl 2-{[(4-methylphenyl)-sulfonyl]methyl}benzoate* **126b** (26.61 g; 52 %) as a solid, m. p. 93 °C, (*lit.*[125] m. p. 92-93 °C), ν_{max} (N) 2953, 2925, 2854, 1713, 1596, 1460, 1408, 1377, 1310, 1295, 1268, 1248, 1197, 1161, 1142, 1121, 1110, 1078, 1034, 1017, 902, 819, 775 and 712 cm^{-1}, δ_H 1.35 (3H, t, *J* 7.0, CH_2CH_3), 2.43 (3H, s, Ph-CH_3), 4.21 (2H, q, *J* 7.3, CH_2CH_3), 5.07 (2H, s, SO_2CH_2), 7.24 (2H, d, *J* 8.5, *H*-3' and *H*-5'), 7.33 (1H, d, *J* 7.5, *H*-3), 7.38-7.55 (4H, m, *H*-4, *H*-5, *H*-2' and *H*-6') and 7.91 (1H, dd, *J* 7.5 and 1.5, *H*-6) ppm, δ_C (100.6 MHz) 13.67 (CH_2CH_3), 21.18 (CH_3), 58.77 (SO_2CH_2), 60.73 (CH_2CH_3), 128.21 (*C*-2' and *C*-6'), 128.28 (*C*-5), 128.80 (*C*-1), 128.96 (*C*-3' and *C*-5'), 130.47 (*C*-6), 130.70 (*C*-2), 131.49 (*C*-4), 133.00 (*C*-3), 135.02 (*C*-1'), 144.02 (*C*-4') and 166.30 (*C*O_2H) ppm.

General procedure for reactions between ethyl 2-{[(4-methylphenyl)sulfonyl]-methyl}benzoate 126b and an aldehyde:

Ethyl 2-{[(4-methylphenyl)sulfonyl]methyl}benzoate **126b** (1.28 g; 4 mmol) in dry DMF (5 mL) was added to ethanolic sodium ethoxide (1M; 12 mmol; 12 mL) at room temperature. After 5 min an aldehyde (4 mmol; dissolved in a little DMF) was added and the mixture was stirred for 1 h. It was then diluted with water and neutral products and residual starting materials were extracted using ether. The aqueous phase was then acidified to pH 1 using diluted hydrochloric acid and extracted using ethyl acetate to give acidic products. Each of these organic extracts was washed with brine, dried and evaporated.

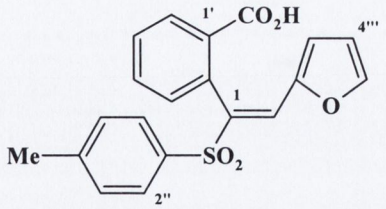
2-{(*E*)-1-[(4-Methylphenyl)sulfonyl]-2-phenylvinyl}benzoic acid 267



267

From benzaldehyde **170** (0.43 g; 4 mmol) there was obtained, after recrystallisation from ethyl acetate, *2-{(E)-1-[(4-methylphenyl)sulfonyl]-2-phenylvinyl}benzoic acid* **267** (1.13 g; 74 %) as white crystals, m. p. 198-199 °C, ν_{max} (N) 2953, 2923, 2853, 2670, 1696, 1656, 1630, 1595, 1571, 1491, 1451, 1418, 1377, 1301, 1288, 1141, 1082, 943, 920, 810, 752, 712 and 676 cm^{-1}, δ_H 2.26 (3H, s, PhCH_3), 7.04-7.12 (5H, m, *H*-3', *H*-3", *H*-5", *H*-2"' and *H*-6"'), 7.20 (2H, t, *J* 7.5, *H*-3"' and *H*-5"'), 7.27 (1H, t, *J* 7.3, *H*-4"'), 7.42 (2H, d, *J* 8.0, *H*-2" and *H*-6"), 7.49-7.53 (2H, m, *H*-4' and *H*-5'), 7.95 (1H, s, *H*-2) and 8.05 (1H, m, *H*-6') ppm, δ_C (100.6 MHz) 21.05 (Ph-*C*H_3), 128.11 (*C*-3"' and *C*-5"'), 128.46 (*C*-2" and *C*-6"), 128.96 (*C*-3" and *C*-5"), 129.06 (*C*-5'), 129.45 (*C*-4"'), 129.80 (*C*-2"' and *C*-6"'), 130.53 (*C*-1'), 130.97 (*C*-6'), 132.04 (*C*-2'), 132.59 (*C*-3'), 132.68 (*C*-4'), 132.77 (*C*-1"'), 134.69 (*C*-1"), 137.15 (*C*-2), 139.84 (*C*-1), 143.98 (*C*-4") and 170.40 (*C*O_2H) ppm, HRMS (CI) *m/z* 401.0805: *calculated for* $[C_{22}H_{18}O_4S+Na]^+$ 401.0824, *calculated for* $C_{22}H_{18}O_4S$: C 69.82, H 4.79; *found* C 69.67, H 4.74 %.

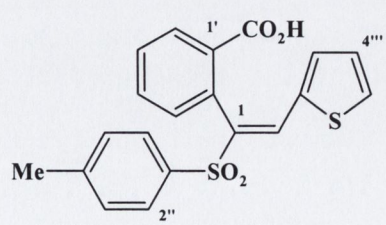
2-{(*E*)-2-(2-Furyl)-1-[(4-methylphenyl)sulfonyl]vinyl}benzoic acid 268



268

From 2-furaldehyde **110** (0.40 g; 4 mmol) there was obtained, after recrystallisation from ethanol, *2-{(E)-2-(2-furyl)-1-[(4-methylphenyl)sulfonyl]vinyl}benzoic acid* **268** (1.38 g; 94 %) as a yellow solid, m. p. 198 °C (decomp.), ν_{max} (N) 2953, 2924, 2854, 2651, 1692, 1673, 1630, 1594, 1572, 1458, 1413, 1377, 1317, 1303, 1276, 1245, 1199, 1149, 1086, 1026, 963, 919, 885, 817, 775, 740, 707, 665 and 657 cm^{-1}, δ_H (DMSO-d_6) 2.36 (3H, s, Ph-CH_3), 6.26 (1H, d, *J* 3.5, *H*-3'''), 6.46 (1H, dd, *J* 3.5 and 2.0, *H*-4'''), 6.74 (1H, dd, *J* 7.5 and 1.5, *H*-3'), 7.32 (2H, d, *J* 8.0, *H*-3'' and *H*-5''), 7.43 (2H, d, *J* 8.0, *H*-2'' and *H*-6''), 7.49 (1H, dt, *J* 7.5, 7.5 and 1.5, *H*-4'), 7.55 (1H, dt, *J* 7.5, 7.5 and 1.0, *H*-5'), 7.63 (1H, d, *J* 1.5, *H*-5'''), 7.64 (1H, s, *H*-2), 7.97 (1H, dd, *J* 7.8 and 1.3, *H*-6') and 12.69 (1H, s, CO_2H) ppm, δ_C (100.6 MHz, DMSO-d_6) 21.09 (Ph-CH_3), 112.50 (*C*-4'''), 116.23 (*C*-3'''), 124.67 (*C*-2), 128.13 (*C*-2'' and *C*-6''), 129.46 (*C*-5'), 129.61 (*C*-3'' and *C*-5''), 130.62 (*C*-6'), 131.63 (Ph*C*), 131.76 (*C*-3'), 131.83 (*C*-4'), 132.30 (Ph*C*), 135.99 (Ph*C*), 137.44 (Ph*C*), 144.03 (*C*-4''), 146.12 (*C*-5'''), 149.06 (*C*-2''') and 166.72 (CO_2H) ppm, HRMS (CI) *m/z* 391.0607: *calculated for* $[C_{20}H_{16}O_5S+Na]^+$ 391.0616, *calculated for* $C_{20}H_{16}O_5S$: C 65.20, H 4.38; *found* C 65.22, H 4.35 %.

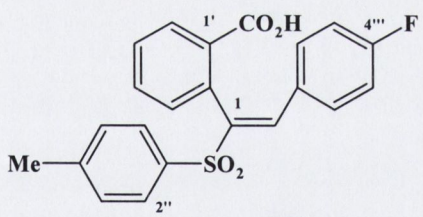
2-[(*E*)-1-[(4-Methylphenyl)sulfonyl]-2-(2-thienyl)vinyl]benzoic acid 269



269

From thiophene-2-carboxaldehyde **220** (0.45 g; 4 mmol) there was obtained, after recrystallisation from EtOAc, *2-[(E)-1-[(4-methylphenyl)sulfonyl]-2-(2-thenyl)-vinyl]benzoic acid* **269** (0.78 g; 51 %) as an off-white solid, m. p. 236-237 °C (decomp.), ν_{max} (N) 2952, 2924, 2854, 2649, 1688, 1671, 1624, 1592, 1571, 1459, 1418, 1376, 1316, 1302, 1277, 1244, 1218, 1147, 1084, 1054, 955, 934, 918, 887, 855, 818, 807, 775, 705, 672, 653 and 623 cm^{-1}, δ_H (DMSO-d_6) 2.37 (3H, s, PhCH_3), 6.71 (1H, dd, *J* 7.5 and 1.0, *H*-3'), 7.04 (1H, t, *J* 4.3, *H*-4'''), 7.33 (2H, d, *J* 8.0, *H*-3'' and *H*-5''), 7.45 (2H, d, *J* 8.0, *H*-2'' and *H*-6''), 7.50-7.57 (3H, m, *H*-4', *H*-3''' and *H*-5'''), 7.61 (1H, dt, *J* 7.5, 7.5 and 1.0, *H*-5'), 8.02 (1H, dd, *J* 7.5 and 1.0, *H*-6'), 8.07 (1H, s, *H*-2) and 12.72 (1H, s, CO_2H) ppm, δ_C (100.6 MHz, DMSO-d_6) 21.12 (Ph-CH_3), 127.09 (*C*-4'''), 128.12 (*C*-2'' and *C*-6''), 129.64 (*C*-3'' and *C*-5''), 130.22 (*C*-5'), 130.81 (*C*-1'), 130.92 (*C*-2), 131.16 (*C*-6'), 131.99 (PhCH or thienyl CH), 132.48 (PhCH or thienyl CH), 132.53 (*C*-3'), 132.99 (*C*-2'), 134.85 (PhCH or thienyl CH), 136.14 (*C*-1''), 136.68 (*C*-2'''), 137.47 (*C*-1), 143.97 (*C*-4'') and 166.53 (CO_2H) ppm, HRMS (CI) *m/z* 407.0395: *calculated for* $[C_{20}H_{16}O_4S_2+Na]^+$ 407.0388, *calculated for* $C_{20}H_{16}O_4S_2$: C 62.48, H 4.19; *found* C 62.17, H 4.08 %.

2-{(*E*)-2-(4-Fluorophenyl)-1-[(4-methylphenyl)sulfonyl]vinyl}benzoic acid 270

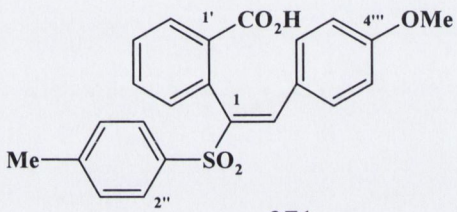


270

From 4-fluorobenzaldehyde **224** (0.51 g; 4 mmol) there was obtained, after recrystallisation from ethanol, *2-{(E)-2-(4-fluorophenyl)-1-[(4-methylphenyl)-sulfonyl]vinyl}benzoic acid* **270** (0.60 g; 38 %) as white crystals, m. p. 208-210 °C, ν_{max} (N) 2952, 2926, 2855, 2670, 2564, 1695, 1636, 1597, 1573, 1510, 1459, 1428, 1416, 1377, 1309, 1240, 1143, 1083, 1017, 970, 946, 932, 904, 830, 810, 779, 712, 673 and 657 cm^{-1}, δ_H 2.31 (3H, s, Ph-CH_3), 6.89 (2H, t, *J* 8.8, *H*-3''' and *H*-5'''), 6.97 (1H, dd, *J* 7.5 and 1.0, *H*-3'), 7.08 (2H, dd, *J* 9.0 and 5.5, *H*-2''' and *H*-6'''), 7.14 (1H, d, *J* 8.6, *H*-3'' and *H*-5''), 7.43 (1H, d, *J* 8.5, *H*-2'' and *H*-6''), 7.50 (1H, dt,

J 7.5, 7.5 and 1.5, *H*-4'), 7.55 (1H, dt, *J* 7.5, 7.5 and 1.5, *H*-5'), 7.92 (1H, s, *H*-2) and 8.06 (1H, dd, *J* 7.8 and 1.3, *H*-6') ppm, δ_C (100.6 MHz) 21.07 (Ph-*C*H_3), 115.30 (d, *J* 21.4, *C*-3''' and *C*-5'''), 128.44 (*C*-2'' and *C*-6''), 128.99 (*C*-3'' and *C*-5''), 129.17 (*C*-5'), 130.71 (Ph*C*), 131.03 (*C*-6'), 131.75 (d, *J* 8.7, *C*-2''' and *C*-6'''), 132.45 (*C*-3'), 132.70 (*C*-4'), 134.64 (Ph*C*), 135.91 (*C*-2), 139.54 (Ph*C*), 144.05 (*C*-4''), 162.91 (d, *J* 252.7, *C*-4''') and 170.42 (*C*O_2H) ppm, δ_F (376.4 MHz) –109.99 ppm, HRMS (CI) *m/z* 815.1594: *calculated for* $[C_{44}H_{34}F_2O_8S_2+Na]^+$ 815.1561, *calculated for* $C_{22}H_{17}FO_4S$: C 66.65, H 4.32; *found* C 66.56, H 4.32 %.

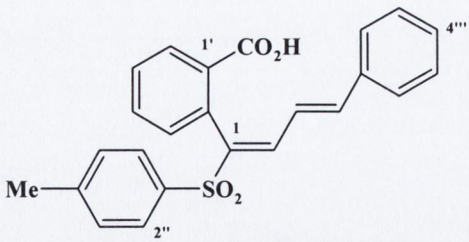
2-{(*E*)-2-(4-Methoxyphenyl)-1-[(4-methylphenyl)sulfonyl]vinyl}benzoic acid 271



271

From 4-methoxybenzaldehyde **241** (0.55 g; 4 mmol) there was obtained, after recrystallisation from ethanol, *2-{(E)-2-(4-methoxyphenyl)-1-[(4-methylphenyl)-sulfonyl]vinyl}benzoic acid* **271** (1.19 g; 73 %) as white crystals, m. p. 192-194 °C, ν_{max} (N) 2953, 2922, 2854, 2663, 2557, 1687, 1625, 1599, 1569, 1513, 1459, 1422, 1377, 1311, 1260, 1184, 1141, 1118, 1083, 1023, 973, 948, 931, 891, 831, 815, 803, 780, 751, 732, 712 and 664 cm^{-1}, δ_H (DMSO-d_6) 2.36 (3H, s, Ph-CH_3), 3.69 (3H, s, OCH_3), 6.57 (1H, d, *J* 7.5, *H*-3'), 6.79 (2H, d, *J* 8.5, *H*-3''' and *H*-5'''), 7.06 (2H, d, *J* 9.0, *H*-2''' and *H*-6'''), 7.31 (2H, d, *J* 8.0, *H*-3'' and *H*-5''), 7.39-7.47 (3H, m, *H*-4', *H*-2'' and *H*-6''), 7.54 (1H, dt, *J* 7.5, 7.5 and 1.0, *H*-5'), 7.78 (1H, s, *H*-2), 7.98 (1H, d, *J* 7.5, *H*-6') and 12.79 (1H, s, CO_2H) ppm, δ_C (100.6 MHz, DMSO-d_6) 21.08 (Ph-*C*H_3), 55.23 (O*C*H_3), 114.07 (*C*-3''' and *C*-5'''), 125.50 (Ph*C*), 128.02 (*C*-2'' and *C*-6''), 129.55 (*C*-5', *C*-3'' and *C*-5''), 130.73 (*C*-6'), 131.74 (Ph*C*), 131.88 (*C*-3'), 131.92 (*C*-2''' and *C*-6'''), 132.14 (*C*-4'), 133.30 (Ph*C*), 136.20 (Ph*C*), 136.53 (*C*-2), 138.33 (Ph*C*), 143.82 (*C*-4''), 160.52 (*C*-4''') and 167.08 (*C*O_2H) ppm, HRMS (CI) *m/z* 839.1989: *calculated for* $[C_{46}H_{40}O_{10}S_2+Na]^+$ 839.1961, *calculated for* $C_{23}H_{20}O_5S$: C 67.63, H 4.94; *found* C 67.42, H 4.85 %.

2-{(1*E*,3*E*)-1-[(4-Methylphenyl)sulfonyl]-4-phenylbuta-1,3-dien-1-yl}benzoic acid 272



272

From (*E*)-cinnamaldehyde **251** (0.53 g; 4 mmol) there was obtained, after recrystallisation from benzene, *2-{(1E,3E)-1-[(4-methylphenyl)sulfonyl]-4-phenylbuta-1,3-dien-1-yl}benzoic acid* **272** (0.97 g; 60 %) as a light-yellow solid, m. p. 84-88 °C, ν_{max} (N) 2952, 2923, 2854, 2670, 1679, 1620, 1596, 1458, 1377, 1315, 1301, 1144, 1083, 973, 927, 887, 815, 751, 708 and 675 cm^{-1}, δ_H 2.32 (3H, s, Ph-C*H*$_3$), 6.37 (1H, dd, *J* 15.6 and 11.0, *H*-3), 7.05 (1H, d, *J* 15.5, *H*-4), 7.09 (1H, m, *H*-3'), 7.17 (1H, d, *J* 8.0, *H*-3" and *H*-5"), 7.25-7.35 (5H, m, *H*-2"', *H*-3"', *H*-4"', *H*-5"' and *H*-6"'), 7.46 (1H, d, *J* 8.5, *H*-2" and *H*-6"), 7.52-7.58 (2H, m, *H*-4' and *H*-5'), 7.69 (1H, d, *J* 11.6, *H*-2) and 8.04 (1H, m, *H*-6) ppm, δ_C (100.6 MHz) 21.08 (Ph-*C*H$_3$), 122.40 (*C*-3), 126.93 (Ph*C*H), 128.24 (Ph*C*H, *C*-2" and *C*-6"), 128.81 (*C*-5'), 128.98 (Ph*C*H, *C*-3" and *C*-5"), 130.72 (*C*-6'), 130.97 (Ph*C*), 131.01 (Ph*C*), 131.89 (*C*-4'), 132.92 (*C*-3'), 135.32 (Ph*C*), 135.45 (Ph*C*), 138.15 (*C*-2), 139.65 (Ph*C*), 141.91 (*C*-4), 143.84 (*C*-4") and 169.42 (*C*O$_2$H) ppm, HRMS (CI) *m/z* 427.0971: *calculated for* $[C_{24}H_{20}O_4S+Na]^+$ 427.098, *calculated for* $C_{24}H_{20}O_4S$: C 71.27, H 4.98; *found* C 70.98, H 5.01 %.

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