Studies towards a total synthesis of Hippeastrine

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4769139

Acknowledgements

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In the loving memory of Sarah Delf, devoted friend and colleague. Wherever you are you always will be remembered. Rest in peace my amazing friend and fellow Hippeastrine crew member.

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Abstract

Tricarbonyl(η^5-carboxylic acid methyl ester)iron(1+) hexafluorophosphate(1−) (**97**) was easily prepared in a moderate yield by a tandem Wittig-Michael addition using (3-methoxycarbonylallyl)triphenylphosphonium bromide (**94**). The resulting cyclohexa-1,3-dienecarboxylic acid methyl ester (**95**) was complexed with $Fe_2(CO)_9$ to obtain tricarbonyl(cyclohexa-1,3-dienecarboxylic acid methyl ester)iron(0) (**96**) was converted into the highly electrophilic tricarbonyl(η^5 -carboxylic acid methyl ester)iron(1+) hexafluorophosphate(1−) by hydride abstraction using triphenylcarbenium hexafluorophosphate (**97**).

4-Bromo-1,2-(methylenedioxy)benzene (**132**), 6-bromopiperonylic acid (**98**) and 2-bromo-5-methoxy benzoic acid (**140**) were converted into aryllithium reagents through lithium-bromide exchange by treatment with *n*-butyllithium. Lithiation and deuteration of 6-bromopiperonylic acid (**98**) , 2-bromobenzoic acid (**136**) and of 2-bromo-5-methoxybenzoic acid (**140**) were investigated by using various reagents such as *n*-butyllithium, LiHMDS and NaH to find the best route for the arylation of **98** to go onwards our target (+/−)-hippeastrine (**107** and **108**).

Tricarbonyl[η^4-1-methyl ester-5-(3',4'-methylenedioxy)phenylcyclohexa- 1,3-diene]iron(0) (**134**) was prepared by preparing the aryllithium reagent **132** by lithium-bromide exchange and converting it into an organocuprate nucleophile with copper(I) bromide. Arylation with the cation **97** resulted in the formation of the complex **134**. Tricarbonyl[η^4-1-methyl ester-5-(3',4'-methylenedioxy-6'-carboxyphenyl)cyclohexa- 1,3-diene]iron(0) (**99**) was synthesised in the same way as complex (**134**), using the lithiated 6-bromopiperonylic acid (**98**) as the reagent. The structures of the compounds were determined by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and mass spectrometry.

1.Introduction

Natural products have been a source of novel active compounds for many decades and have been used as lead molecules as well as scaffolds for elaboration of a great many potent drugs for the treatment of various diseases.[1] Classical natural product examples are found among anticancer (e.g. paclitaxel also known as Taxol derived from yew bark tree)[2], antiparasitic (e.g. artemisinin isolated from a Chinese herb called sweet wormwood that is used as a lead compound for antimalarial treatment)[3] and antibacterial drugs (e.g. fosfomycin trometamol, also known as Monuril, which is an antibiotic used to treat acute uncomplicated urinary tract infections). Alkaloids are nitrogen containing natural products with low molecular weight and are widely found in nature, most often in plants and have interesting pharmacological properties. The biological activity of many alkaloids often relies on the amine being transformed into a quaternary ammonium ion, by protonation at physiological pH values.[4]

Hippeastrine, is a member of the alkaloid family and possesses numerous pharmacological properties. From a purely synthetic point of view, hippeastrine possesses key structural elements that make it an attractive challenge for synthetic organic chemists due to the number of synthetic approaches that can be envisaged. The structural properties and synthetic strategies will be explained and developed later on in this chapter. This project aims towards the synthesis of hippeastrine (for which a model study has already been achieved by Stephenson's group[5]), taking advantage of the available tricarbonyl iron and organo cuprate chemistry in order to build hippeastrine's A,B,C ring model system (**Figure 1**).

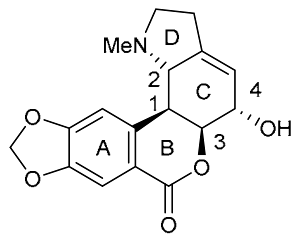

Figure 1: Hippeastrine

1.1. History of Alkaloids

Alkaloids are compounds that are widely occurring in nature and are typically extracted from plants but can also be found in other organisms. Some frogs for example produce toxic alkaloids in the skin or secretory glands, and insects such as ants use alkaloids as pheromones. Fungi are also a source of alkaloids.[6] These living organisms have over thousands of years developed the production of alkaloids as defences against herbivores, carnivores, microorganisms or viruses and hence have developed alkaloids exhibiting a wide range of properties.[7] The first evidence that humankind used alkaloid-producing plants was described in Assyrian clay tablet written in cuneiform characters four thousand years ago. These tablets described about 250 different plants including a number of alkaloid-containing plants such as *Papaver somnifirum* known as opium poppy and *Atropa belladonna* known as deadly nightshade.[7] The term alkaloid was coined by the German Carl Friedrich Wilhelm Meissner in 1819 to refer to plant natural products showing basic properties similar to those of the inorganic alkalis.[8] The first isolation of an alkaloid was achieved by French apothecary Derosne in 1803[9] who isolated narcotine (**Figure 2**), before Sertürner further investigated alkaloids by isolating opium[9] (**Figure 3**) in 1806 and morphine (**Figure 3**) in 1816. Other alkaloids such as strychnine (1817), emetine (1817), brucine (1819), piperine (1819), caffeine (1819), quinine (1820), colchicine (1820) and coniine (1826) were isolated by Pelletier and Caventou.[9] Coniine was the first alkaloid to have its structure established by Schiff in 1870 and to be synthesized by Ladenburg in 1889.[9]

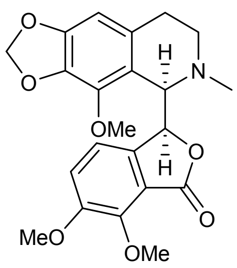

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Figure 2: Narcotine Structure

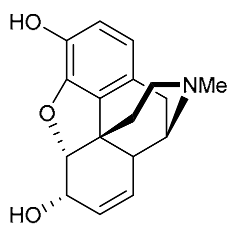

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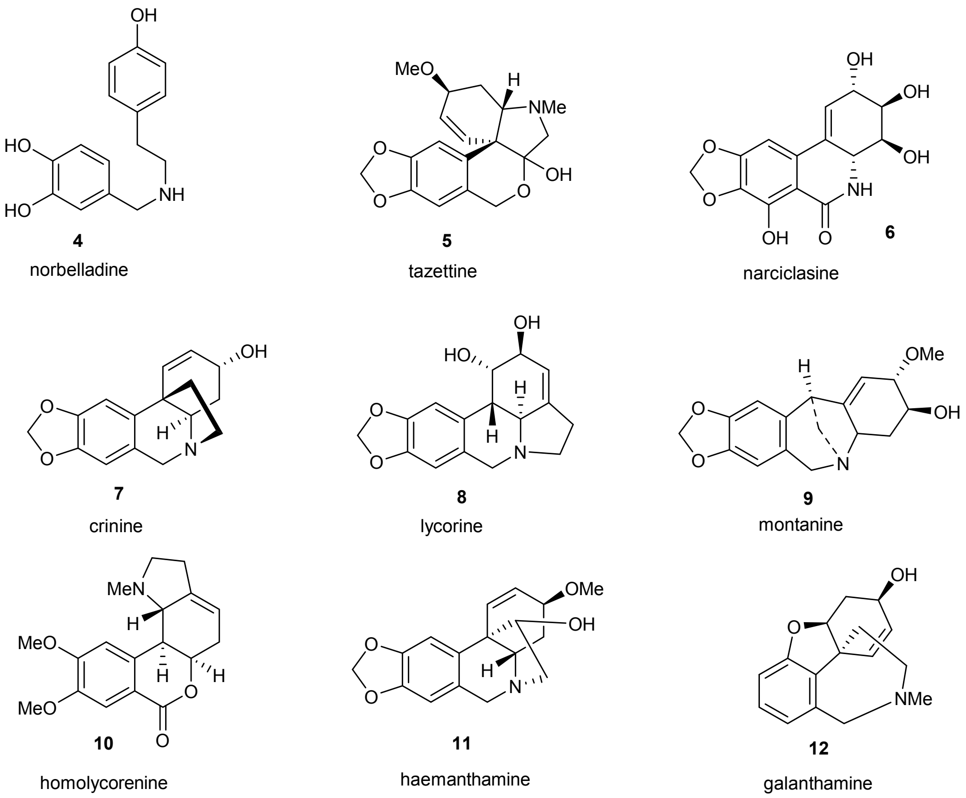
Figure 3: Opium and morphine Structure

1.2. Amaryllidaceae Alkaloids

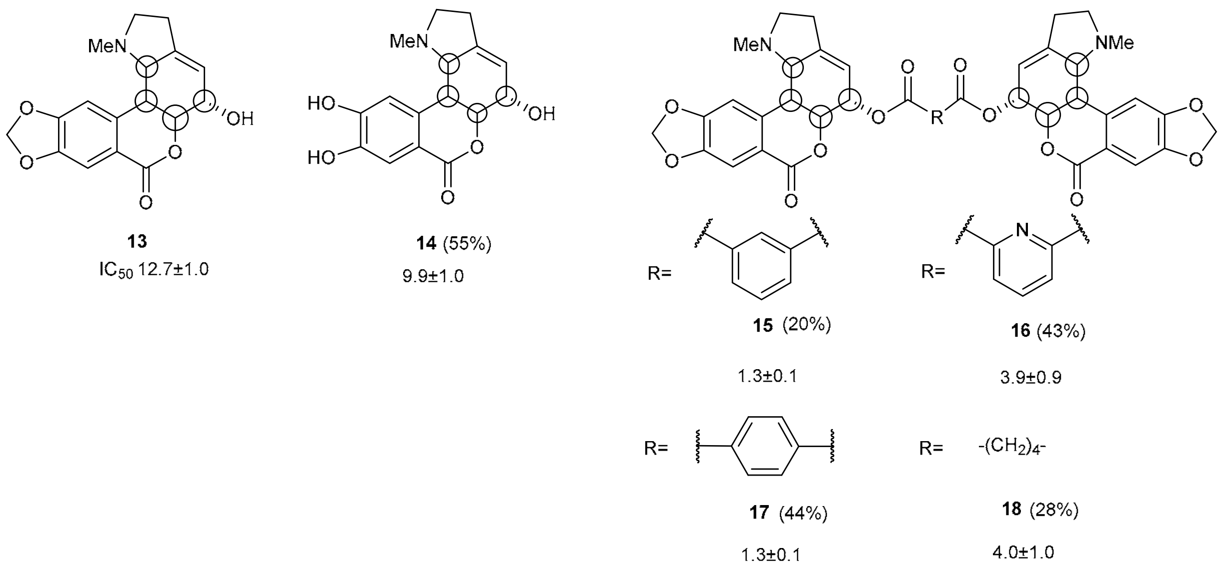
Around 12,000 different alkaloids distributed over a number of distinct classes have been identified in plants, and many of them possess potent effects in the treatment of several human medical conditions. The Amaryllidaceae produce a class of alkaloids that is notably occuring in a range of families of bulbous plants: *Galanthus* (snowdrops), *Narcissus* (daffodils) genera and many other bulbous species.[10] Amarylladiceae is composed of around 1100 species in *circa* 85 genera that are widely distributed throughout the tropics and warm temperate regions of the world. These alkaloids form a unique class of nitrogen-containing compound showing promising biological activities such as galanthamine (commercially known as Reminyl), an acetylcholinoesterase inhibitor used in the treatment of Alzheimer's disease[11] and lycorine that shows antiinflamatory[12] as well as antimalarial properties.[13] Lycorine, amarbellisine, haemanthamine and haemanthidine also exhibit important activity against apoptosis-resistance on six different cancer cell lines.[14] Pancratistatin and narciclasine have also been shown to possess promising antitumor activity.[15] The Amaryllidaceae alkaloids are classified according to their main skeletal structure and named after a representative alkaloid from each class. They are classified into nine main subgroups.[10]



Scheme 1: The Amaryllidaceae alkaloid family subgroups

1.3. Function and Synthesis of the Alkaloid Hippeastrine

The homolycorenine-type hippeastrine, an alkaloid from the Amaryllidaceae family is isolated from genera such as *Brunsvigia*, *Crinum*, *Boophane* or the genus *Pancratium* which contains over 21 species distributed around the Mediterranean region.[16] *Pancratium canariense*, a white bulbous flower usually found in Canary Islands, is the main source of hippeastrine. In 2009, Cedrón's group was the first group to investigate and extract hippeastrine (1.35 g) among other amaryllidaceae alkaloids from *Pancratium canariense*.[17] Hippeastrine possesses some potent biological activities, Evidente *et al*.[18] tested the anticancer activity of hippeastrine and other Amaryllidaceae alkaloids and concluded that hippeastrine has antiproliferative activities and inhibits cell growth *in vitro* at nontoxic concentrations. It was also found to display antiviral activity against *Herpes simplex* virus (HSV) type 1 due to the hexahydrolindole ring which has a direct effect on virus multiplication,[19] and antifungal activity against *Candida albicans* a fungus responsible for unpleasant symptoms such as athlete's foot and thrush for humankind.[20] Modifications performed on hippeastrine **13** gave a series of analogues which were tested for their potent antimalarial activity and it was found that the hippeastrine derivative that lacked the methylenedioxy moiety **14** showed a slight increase in activity compared to the parent molecule **13**. The activity of the different dimers (**15**, **16**, **17**, **18**) of hippeastrine showed a 10-fold increase compared to hippeastrine (**13**). The fact that the dimers are more potent than the monomers could suggest an improvement of the dimers' binding to the specific target or potential hydrolysis of the dimer giving two molecule of hippeastrine during the biological outcome.[21]

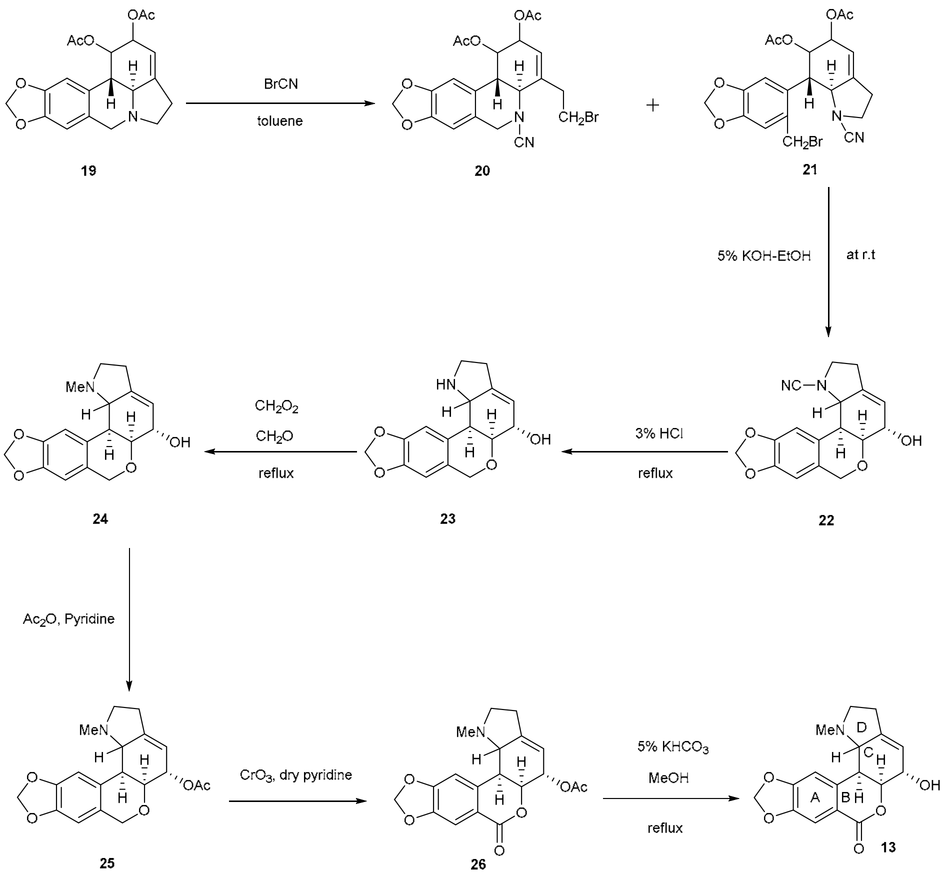


Scheme 2: Antimalarial activity (in μM) of hipeastrine analogues

Hippeastrine (**13**) possesses several structural key elements: four stereogenic centres, a methylenedioxy group and a lactone ring B. The hydroxyl in the C ring and the tertiary amine in the 5-membered D ring are orientated *cis* to each other, whilst being *trans* to the two bonds connecting rings B and C (**Figure 1**).

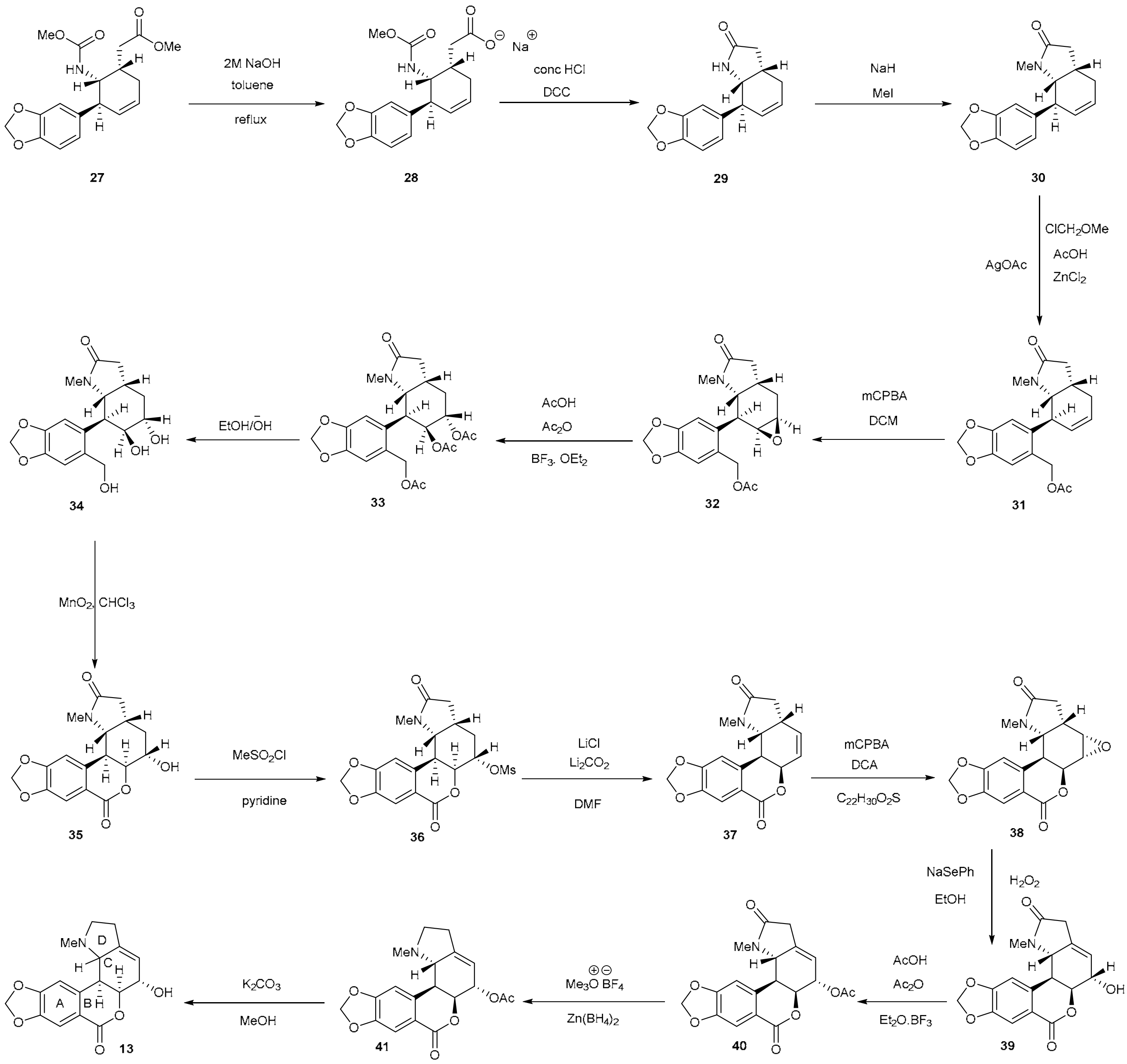
1.3.1. Synthesis of Hippeastrine

Two major groups have synthesised hippeastrine, Kotera's and Katakawa's. In 1967, Kotera *et al.* reported[22] the synthesis of hippeastrine (**13**) from diacetyllycorine (**19**) in seven steps (**scheme 3**). The von Braun degradation performed on the diacetyllycorine with cyanogen bromide in dry toluene afforded two products **20** and **21** (detectable in equal intensity as poorly isolable spots on TLC plate) obtained in 100% yield. They differed by a rotation of **21** around the single bond between ring A and C was performed. Subsequent treatment of **21** with 5% ethanolic potassium hydroxide at room temperature allowed the ring closure to occur giving **22** (formation of ring B) in 31% yield. Refluxing **22** with aqueous HCl (3%) afforded the secondary amine **23** in 36% yield. An Eischweiler-Clark reaction installed the N-methyl group on the secondary amine by reflux of **23** with formic acid and formaldehyde giving compound **24** in 87% yield. Acetylation of deoxyhippeastrine **24** was achieved using acetic anhydride and pyridine to give the crude acetate **25** (95% yield) which in turn was reacted with chromium trioxide in dry pyridine afford **26** in 13% yield. Finally, the desired compound **13** was obtained by reflux with 5% potassium bicarbonate in methanol (91% yield).



Scheme 3: Synthesis of Hippeastrine from diacetyllycorine

In 1984, Katakawa and Meguri suggested a synthetic route of (±)-hippeastrine (**Scheme 4**).[23] The starting material urethane-ester **27** was previously used as a starting material in the total synthesis of the Amaryllidaceae alkaloids, lycorine and zephyranthine.[24] In this case, urethane-ester **27** was treated with sodium hydroxide yielding the amino acid sodium salt **28** that was then treated with concentrated HCl and DCC to form the 5-membered ring (**29**, 80% yield) which eventually becomes the D ring of hippeastrine. The next step involved the methylation of the amine in the five-membered ring affording **30** in good yield, followed by the electrophilic alkylation of the aromatic A ring using chloromethyl methyl ether to give the acetoxy-lactam **31** (45% yield). Epoxidation of the double bond in the C ring with *m*-chloroperbenzoic acid in methylene chloride gave **32** as the sole product in 75% yield. Reaction of the epoxide with acetic acid and acetic anhydride in the presence of boron trifluoride etherate effected ring opening and the formation of a triacetate **33** in good yield. Alkaline hydrolysis of the triacetate in ethanol yielded to a triol **34**, and was followed by cyclisation (formation of the lactone ring B) affording **35**. **35** was treated with methanesulfonyl chloride in pyridine giving mesylate **36** which was in turn reacted with lithium chloride and lithium carbonate in dimethyl formamide under anhydrous conditions to yield the dehydro-lactam **37** (85% yield). Epoxidation of the alkene gave compound **38** (80% yield), and conversion of the epoxide into an allylic alcohol using Sharpless conditions[25] afforded **39** (45% yield). Acetate protection of the allylic alcohol gave **40** which was then treated with trimethyloxonium tetrafluoroborate first, followed by zinc borohydride in order to reduce the lactam to the tertiary amine ring D, giving **41** in 13% yield. Hydrolysis of the acetate with potassium carbonate in methanol/water afforded (±)-hippeastrine (**13**).



Scheme 4: Synthesis of the racemic (±)-hippeastrine

1.4. Importance of tricarbonyliron complexes in the synthesis of Alkaloids

Tricarbonyl iron complexes are of high interest in asymmetric synthesis, in particular as precursors to chiral cationic iron complexes. These relatively stable complexes are also important intermediates for the synthesis of fairly complex natural products.[26] Cationic tricarbonyliron moieties react notably with a versatile range of nucleophiles to form new stereogenic centre(s). Moderate to good control of the regioselectivity and complete control of stereoselectivity in this reaction process can be achieved, providing a general access to specific enantiopure diastereoisomers by varying the nature and the position of the substituents attached to the cationic tricarbonyliron complex.[27] Cyclohexadienyliron complexes are thus convenient building blocks for the synthesis of alkaloids. They can be reacted with several aryl moieties, creating a new carbon-carbon bond, and forming the backbone of many alkaloids, often referred to as the "C_{12} central building block".[28]

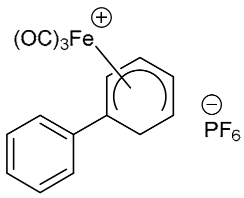


Figure 4: Simple example of "C_{12} building block"

A second nucleophile addition can be used, forming a second carbon carbon bond and in some cases creating quaternary stereogenic centres is possible in this way. In this step, the nature and position of the aryl substituent and other functional groups that are present in the cyclohexadienyliron affect the regiocontrol.[29] When both reactions take place at the same position, this is referred as "*1,1* iterative series"; *O*-methyljoubertiamine and mesembrine are such examples of alkaloids demonstrating this pattern. Reactions at adjacent positions are referred to as "*1,2* iterative series"; hippeastrine and lycorine are examples that display this series.[30]

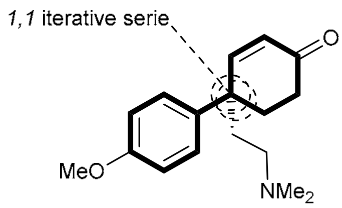


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Figure 5: *1,1* iterative series illustrated by *O*- methyljoubertiamine

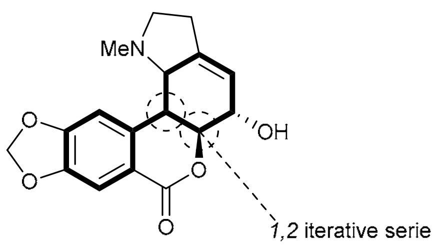

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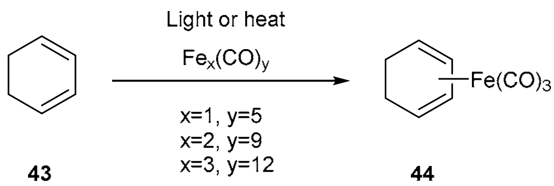
Figure 6: *1,2* iterative series illustrated by hippeastrine

1.4.1. Preparation of tricarbonyliron complexes

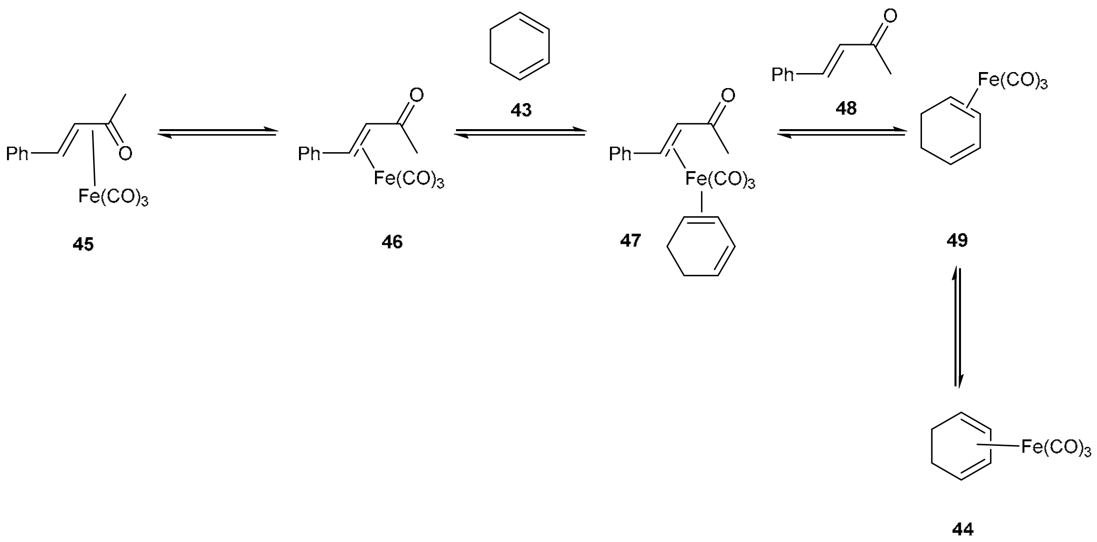
In 1930, Reihlen's group was the first group to report the successful synthesis of a metal-diene transition complex. Using an excess of 1,3-butadiene with pentacarbonyliron in an autoclave for 24 hours at 135-140 °C, he formed tricarbonyl (η^4-buta-1,3-diene)iron in 15% yield.[31] Then in 1958, Pauson and Hallam synthesised for the first time a tricarbonyl(η^4-cyclohexadiene)iron complex in 21% yield, using the original procedure of Reilhen.[32] Since then, the traditional procedures to prepare tricarbonyliron-diene complexes are performed by direct complexation of 1,3-dienes with carbonyliron compounds (pentacarbonyliron, nonacarbonyldiiron, or dodecacarbonyltriiron) under either thermal or photolytic conditions that generate the loss of one or more carbon monoxide molecules.[33]



Scheme 5: synthesis of tricarbonyl(η^4-cyclohexadiene)iron by thermal or photolytic conditions using different carbonyliron compounds

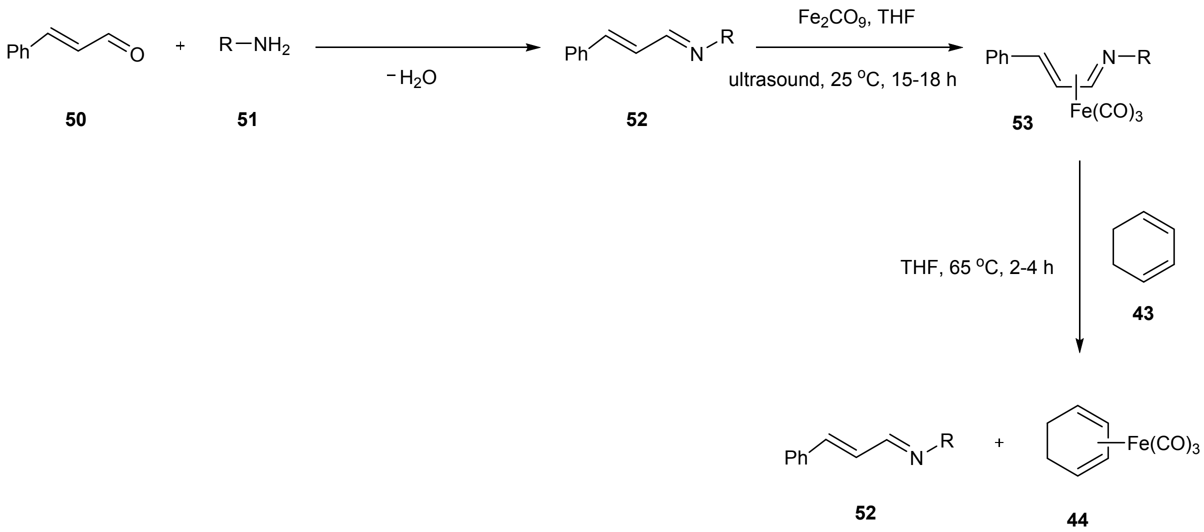
1.4.2. Ligand exchange using transfer reagents.

The complexation of the diene to the metal fragment can be achieved under milder reaction conditions and thus leading to a greater selectivity using tricarbonyliron transfer reagents.[33] These compounds are labile complexes in which the ligand exhibits only a relatively weak coordination to the iron.[34] The development of such tricarbonyliron transfer reagents for the efficient complexation of 1,3-dienes has been largely investigated over the past decades. Weiss' group reported the first synthesis of tricarbonyl-(η^4-1-oxabuta-1,3-diene)iron complexes in 1964 using this method.[35] Among these complexes tricarbonyl(cinnamaldehyde)iron was prepared by heating tetracarbonyl(cinnamaldehyde)iron at 60 °C for 15 hours. These complexes were used as tricarbonyliron transfer reagents for the first time by Lewis in 1972.[33] The (η^4-benzylideneacetone)tricarbonyliron complex, (bda)$Fe(CO)_3$, an example of tricarbonyl-(η^4-1-oxabuta-1,3-diene)iron complex, was obtained in 32% yield by Lewis' group using thermal reaction conditions (heating for 4-5 hours at 60 °C in toluene) by reacting benzylideneacetone with diironnonacarbonyl.[36] In 1991, Thomas' group improved the method by refluxing for 18 hours benzylideneacetone and two equivalents of diironnonacarbonyl in diethyl ether obtaining 81% of the desired compound.[37] Cyclohexa-1,3-diene reacts with (bda)Fe(CO)$_3$ in benzene to produce the tricarbonyl(η^4-cyclohexadiene)iron in almost quantitave yield.[38] This reaction clearly demonstrates the utility of such tricarbonyliron transfer reagents, as they give the desired triironcarbonyl complexes in much higher yield than the traditional method.



Scheme 6: Mechanism for the transfer of the tricarbonyliron fragment from (η^4- benzylideneacetone)tricarbonyliron to cyclohexa-1,3-diene

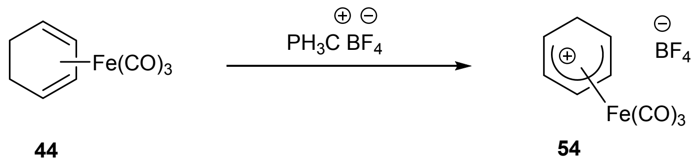
When increasing the reaction temperature, complex **45** undergoes a haptotropic rearrangement to form (η^2- benzylideneacetone)tricarbonyliron (**46**). Coordination of the iron atom to one of the double bonds of cyclohexa-1,3-diene (**43**) forms (η^2-benzylideneacetone)tricarbonyl(η^2-cyclohexa-1,3-diene)iron (**47**). This complex is very unstable and generates the loss of benzylideneacetone (**48**) to yield tricarbonyl(η^2-cyclohexa-1,3-diene)iron (**49**) followed by another haptotropic migration to produce the desired tricarbonyl(η^4-cyclohexa-1,3-diene)iron complex (**44**). In 1967, Otsuka [39] followed by Lewis in 1972[40] described for the first time (η^4-1-azabuta-1,3-diene)tricarbonyliron complexes as a novel class of transfer reagents due to their great stability in air and their greater lability. These useful tricarbonyliron transfer reagents are usually easily prepared in high yield by condensation of cinnamaldehyde (**50**) and the amino compound **51** to result in the formation 1-azabuta-1,3-dienes **52**. Sonication of the 1-azabuta-1,3-dienes **52** in the presence of nonacarbonyldiiron gives transfer reagent **53** which can then reacts with cyclohexa-1,3-diene (**43**) at high temperature to achieve the transfer of the metal fragment and provide the tricarbonyliron cyclohexa-1,3-diene complexes (**44**) in excellent yields.[41]



Scheme 7: Synthesis of tricarbonyl(η4- cyclohexa-1,3-diene)iron from azabuta-1,3-dienes

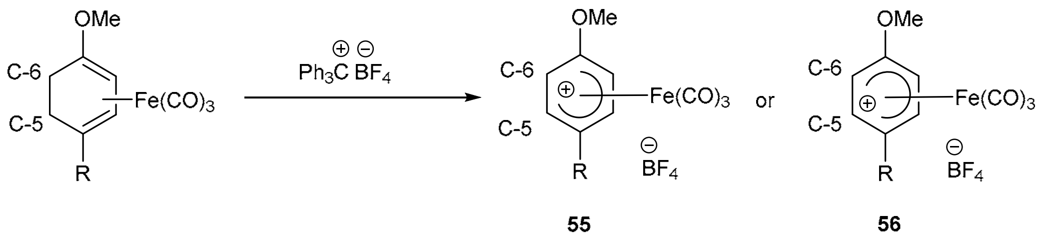
1.4.3 Hydride abstraction

In 1960, Fischer presented for the first time the hydride abstraction of a triironcarbonyl complex, (**scheme 8**, **44**). Addition of triphenylcarbenium tetrafluoroborate (Ph_3CBF_4) to complex **44** resulted in the removal of a hydride ion subsequently affording tricarbonyl(η^5-cyclohexadienylium)iron tetrafluoroborate (**54**).[42]



Scheme 8: Hydride abstraction of tricarbonyl(η4-cyclohexa-1,3-diene)iron complex

Hydride abstraction from substituted cyclohexadiene complexes has been extensively examined by Birch's group, commencing in 1973. Different regioisomers were obtained in various ratios and these ratios were found to depend on the steric demand, electronic properties and position of the substituent groups on the diene and surrounding the hydrogen atom that needed to be removed.[43]



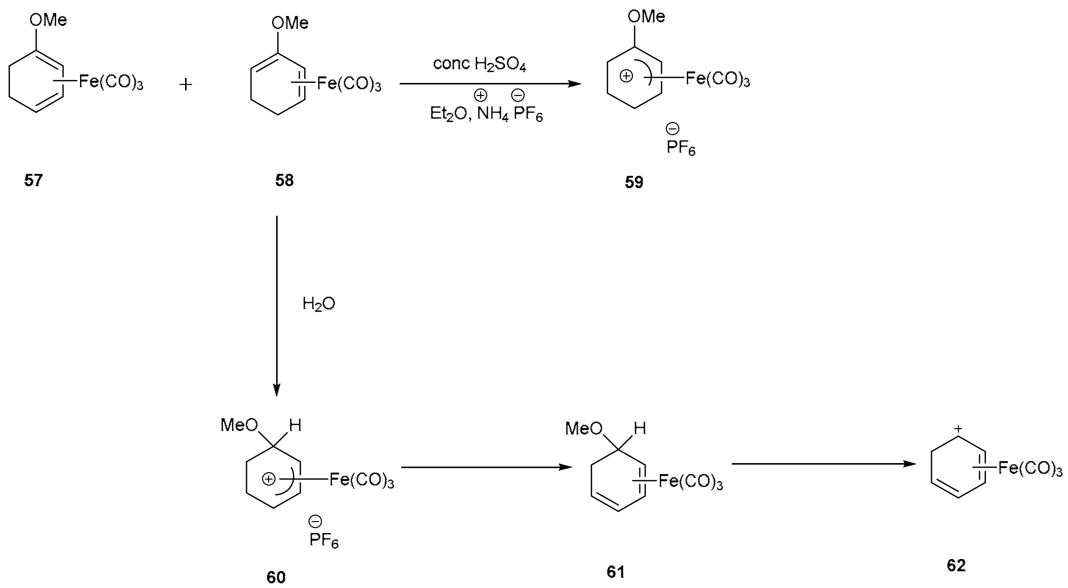
Scheme 9: Hydride abstraction sites

entry	R	Ratio 55:56
1	H	80:20
2	Me	90:10

Table 1 : Ratio of different substituted tricarbonyl(η^5-cyclohexadienylium)iron tetrafluoroborate

In this example (scheme 9, table 1), the hydride abstraction was favoured at C-5 position due to the electron donating nature of the -OMe substituent.

In an alternative approach, 1- and 2-methoxycyclohexa-1,3-diene complexes **57** and **58** were converted into the carbonium salt (**62**) by treatment with concentrated sulfuric acid, followed by ether washes and addition of 10% ammonium hexafluorophosphate.[44]



Scheme 10: Conversion of 1- and 2-methoxycyclohexa-1,3-diene complexes into methyl-substituted tricarbonyl(η^5-cyclohexadienylium)iron salts be demethoxylation using concentratred sulfuric acid

Equilibration of 1- and 2-methoxycyclohexa-1,3-diene or protonotion at the least hindered position of those complexes would result in the formation of the π-allyl complexes (**59**) and the acyclic π-allyl complexes (**60**) which was reported by Pettit and Emmerson in 1962 by a simple water attack .[45] **60** that contains -CHOMe allylic group onto the complexed diene, goes through methanolysis process to protonate OMe, which would give (**62**). The last reaction is irreversible under the conditions. The final step led to the formation of stable carbonium salts in strongly acid media.

1.5. Organocopper reagents

Organocopper reagents provide a general synthetic tool in organic chemistry for carbon-carbon bond formation. Indeed, they readily react with α,β-unsaturated carbonyl compounds via conjugate addition in a 1,4-manner or alternatively they can react via nucleophilic substitution of various groups, epoxide opening and additions to acetylenes.[46]

The first organocoppper reagent was investigated in 1923 by Reich who synthesised unstable phenylcuprate which was prepared from phenyl-magnesium bromide and cuprous iodide.[47] Then, in 1952, Gilman's group obtained organocopper reagents by transmetalation of organolithium reagents with copper(I) halides. The reactions with organolithium reagents generally require a stoichiometric amount of copper salt (one equivalent of copper reagent for two equivalents of lithium reagent), so no free organolithium reagent remains, since the lithium reagent itself is very reactive toward most substrates.[48] Organomagnesium, organozinc and organoboron compounds can also be transmetalated.

$$2\ RLi + CuX \xrightarrow[X=\ I,\ Br,\ Cl]{Et_2O} R_2CuLi + Li^{+}\ X^{-}$$

Scheme 11: Gilman reagent reaction equation

In 1967, Corey and Posner showed that organocopper reagents could be used efficiently for carbon-carbon σ bond formation. Reaction between organic halides and Gilman reagent such as lithium dimethylcopper gave a new carbon-carbon σ bond by displacement of the halide.[49]

1.5.1. High order and low order organocuprates

Organocuprates are important well established synthetic tools in organic chemistry. They have been used in the synthesis of many natural products such as prostaglandin E_2 through a tandem organocopper conjugate addition/alkylation reaction.[50] The synthesis of *O*-methyljoubertiamine and lycoramine have also shown the use of organocopper reagents to provide "C_{12} central building block".[27] Depending on the stoichiometric amount of organolithium reagent LiR (one or two equivalents) added to CuX (X= I, Br, Cl, CN, etc...), two different type of organocuprates can be formed, RCu(X)Li (i.e. the Gilman Reagent) and $R_2Cu(X)Li_2$, respectively. The term ‘‘higher-order’’ ($R_2Cu(X)Li_2$) organocuprates was introduced for the first time in 1984 by Lipshutz *et al.* "High-order cyanocuprate" proved to have a greater reactivity, selectivity and often give better yield than the corresponding "lower order" form.[51]

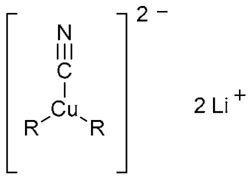


Figure 7a

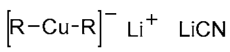
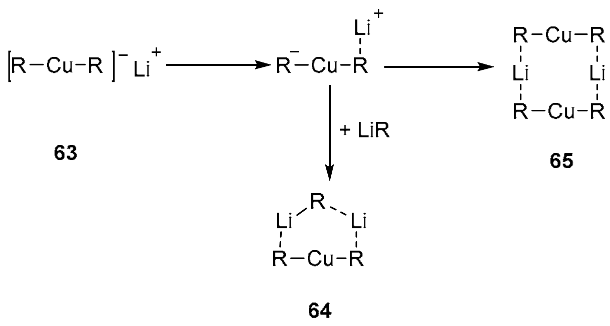


Figure 7b

Lipshutz considered the idea that Cu(I) salts are tricoordinated (Figure 7a). This was the cause of a controversy in the 1990s, as the research community was wondering whether to accept the "higher-order" cyanocuprate concept or not. Many research groups, however, have subsequently confirmed its legitimacy and suggested that the nitrile ligand would be unbound to copper. However, adressing a question raised by Lipshutz: "If the nitrile group is not bounded to the copper, then where is it ?"[52], Bertz *et al.,* using ^{1}H, ^{13}C NMR data, showed that the ^{13}C chemical shifts from phenyl, alkyl, methyl moieties prepared from two equivalents of RLi with one equivalent of CuCN or CuI in THF were similar. MeCuLi.LiCN shows a ^{13}C chemical shift for the methyl group at − 9.51 ppm and the corresponding signal for MeCuLi.LiI is found at − 9.62 ppm.[53] Futhermore, the CN resonances for $R_2Cu(CN)Li_2$ (where R= Ph, Et, Me) were identical, whereas in "lower-order cyanocuprates" (one equivalent of RLi and one equivalent of CuCN), clear changes in the CN chemical shift are observed when the R group is varies.[53] Snyder and Penner-Hahn group's investigated this controversy by studying the infrared spectroscopy of diorganocyanocuprate and came to the same conclusion as Bertz's group.[54] In 1996, Bertz replied to the rhetorical question posed earlier by Lipshutz and James by stating "It's on Lithium!" and therefore suggested a more conventional formula, modified Gilman like species $R_2CuLi.LiCN$ (figure 7b).[55] In 1998, with the support of ^{13}C, ^{6}Li, ^{15}N NMR and crystallographic (EXAFS) data, Bertz ended the controversy of cyano Gilman reagent and concluded that the cyano was not bound to the copper.[56]

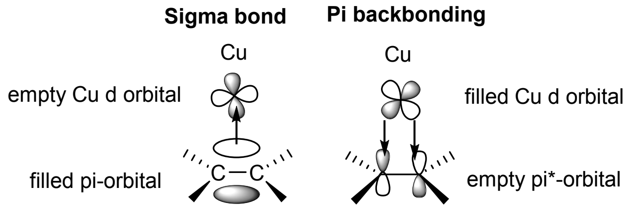
"Lower order" cyanocuprates exist as two main analogues, the symmetric complexes (R_2CuLi) that results from the dissociation of the "higher order" cyanocuprates (see Figure 8b) also called Gilman reagents and unsymmetrical complexes (RCu(CN)Li) which result from the addition of one equivalent of RLi reagent to one equivalent of CuCN. Unsymmetrical "lower order" cyanocuprates have been investigated by Bertz using ^{13}C NMR spectroscopy and those studies showed that at −110 °C the coupling between the methyl and the cyanide carbon group of $^{13}CH_3Cu(^{13}CN)Li$ had a value of 21 Hz which could only be the case if both groups were bound to the same copper atom.[57] These unsymmetrical "lower order" cyano-cuprate complexes were found to be useful in 1,4 additions with α,β-unsaturated ketones, and halide displacement from alkyl halides, since the products of these reactions were obtained in improved yields compared to the ones reported with the symmetrical "lower-order" cyano-cuprate complex.[58] Lithium diorganocopper(I) species (R_2CuLi) are thermally unstable and thus are prepared at low temperatures. Because of their low basicity, diorganocuprates provide alkylation reactions with a variety of organic electrophiles, via S_N2 and S_N2' reactions. Several structures have been proposed for diorganocopper(I) species. It can appear as a linear free organocuprates: $[R_2Cu]^-$ **63**, where the lithium has been sequestrated from the cluster by mixing R_2CuLi with 12-crown-4 solution, which also strongly decelerates the carbocupration reaction. The Li(I) cation and one of the two negative methyl groups are placed in such a fashion from each other that they cannot enjoy favorable electrostatic interaction due to the lack of permanent dipole making the cuprate unreactive in many standard organocopper reactions. [59] R_2CuLi **64** is formed upon coordination of a pair of lithium cations to the linear R-Cu-R anion and an alkyl, phenyl, methyl group that results in a dimerization of RLi and R_2CuLi.[60] $(R_2CuLi)_2$ **65** exists predominantly as a dimer in solution which has been suggested to have a cyclic structure consisting of an alkyl (or aryl) groups bridging a copper and a lithium atom. This structure has been established by NMR spectroscopy and crystallography.[61]



Scheme 12: Possible "lower- order" organocuprate structures

1.5.2. Molecular orbital descriptions of organocopper reagents

The nucleophilic organocopper(I) reagents contain a filled set of d orbitals, with two perpendicular nodal planes that intersect along the internuclear axis. The linear d orbital of copper is more likely to involve an electron pair in a high energy due to the repulsion, hence giving a bent structure to the copper(I) reagent. The simplest representation of the reaction between organocopper reagents and an electrophile is an orbital overlap between an allylic or an alkene orbital and a copper- centred orbital which can be regarded as the result of the interaction of a copper d orbital (HOMO) with the LUMO (π*) of the carbons in the carbon-carbon double bond. This process is commonly called π-backbonding donation due to the electron density that is donated from the π-orbital of the ligand to the empty copper d-orbital to form a σ like bond and as a consequence, the ligand double bond becomes electron deficient which may be remedied by the donation of the copper d-electron pair into the empty π* (antibonding) orbital of the ligand, i.e. the π-backbonding aspect. (**Scheme 13**).[62]



Scheme 13: Molecular Orbital representation between a Copper reagent and a ligand

1.5.3. Organocuprate reagents and the use of additives

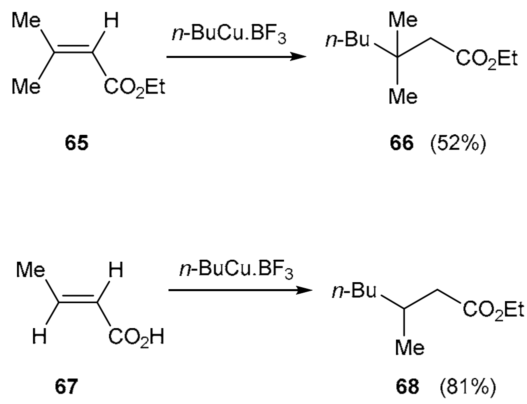
The solubility and reactivity of some organocopper reagents in substitution reactions and conjugate additions to α,β-unsaturated carbonyl compounds have been investigated. These factors are mainly governed by the moderate reactivity of the organocopper reagents or by the steric hindrance of the substrates. These issues are often the source of problems when low yielding reactions are encountered. In 1977, Yamamoto reported that, upon treatment of a neutral organocopper compound with boron trifuoride etherate (BF_3•OEt_2) at low temperature, a reagent was formed with the stoichiometry formula $RCu.BF_3$.[63] A few years later Yamamoto and Ibuka discovered that $AlCl_3$ could also be used to enhance the reactivity of organocopper complexes.[64] Following these using Lewis acids (LAs) with some lower-order cuprates and higher-order cyanocuprate reagents became an effective method for improving carbon-carbon bond formation, however other Lewis acids such as $ZnCl_2$, $TiCl_4$ and $SnCl_4$ were found to be incompatible with high order cuprate reagents due to the formation of intractable gum even at low temperature (−78°C) suggesting a lack of compatibility.[65]

$$RLi + CuX \longrightarrow RCu.LiX \xrightarrow{BF_3.OEt_2} RCu.BF_3 + LiX$$

Scheme 14: equation for the modification of organocopper reagents with boron trifluoride

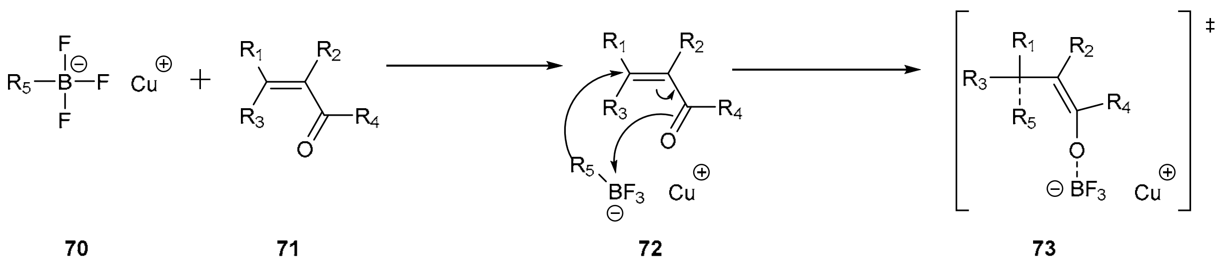
The reactivity of complexes such as RCu.LA is altered by parameters such as the choice of the Lewis Acid (LA=BF_3•OEt_2, $AlCl_3$, etc.), the choice of solvent (THF, diethyl ether, etc.) the choice of copper salt (CuX, where X= Cl, Br, I, CN, etc.) and the stoichiometric amount of organometallic reagent (RM, where M= Li or MgX) to CuX.[64]

Conjugate addition reactions of organocuprate reagents to α,β-unsaturated carbonyl compound are useful synthetic transformations but the attempted conjugate additions to these α,β-unsaturated carbonyl substrates were quite challenging due to poor results reported with conventional dialkylcuprate reagents.[65] These Lewis acid complexes give an efficient conjugate addition to the α,β-enoate esters and α,β-enoic acids affording the 1,4-alkylated esters and acids in good yields.[66]



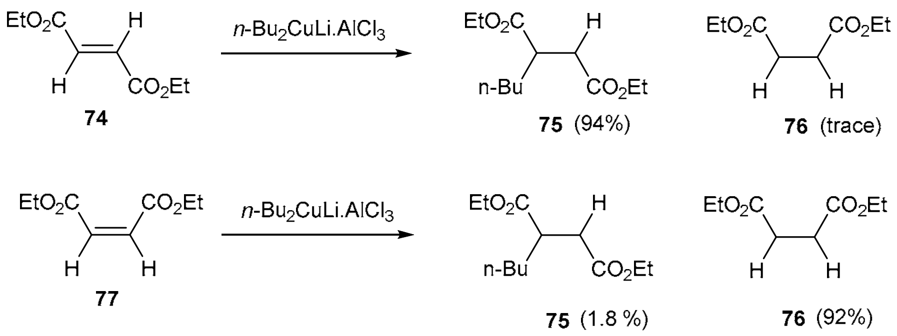
Scheme 15: Conjugate addition to α,β-unsaturated esters and acids

The observation that conjugate addition proceeds well with these Lewis acid activated cuprates can be rationalised by a simple mechanistic proposal (**Scheme 16**). The formation of a transition state **73** would involve the coordination of BF_3 complex with a carbonyl group and therefore trigger the reactivity of the reaction.[66]



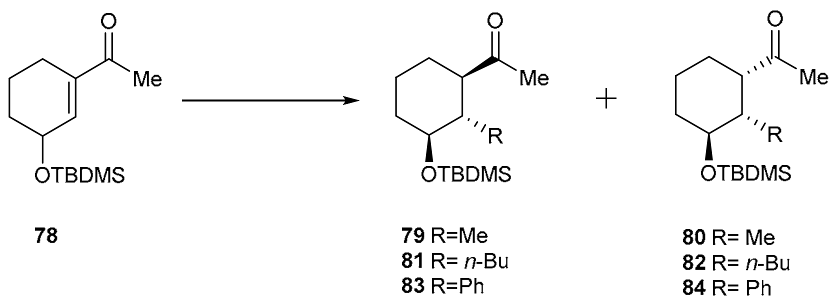
Scheme 16: Formation of the transition state between borontrifluoride and carbonyl substrate

Reactions of alkenes containing electron withdrawing groups with organometallic reagents often yield to a complex mixture of products (see for example the reaction of diethyl fumarate **74** with *n*-Bu_2CuLi, **scheme 15**). The $AlCl_3$ complex gives the conjugate adduct, diethyl butylsuccinate (**75**, 94%), and only a trace amount of the reduced product, diethyl succinate (76). However under these same reaction conditions, diethyl maleate **77** yields predominantely the reduced form **76** and a small amount of the adduct product **75**. This difference in reactivity and direction of the reaction path is dependent upon the geometry of the double bond of the substrate.[67]



Scheme 17: Difference in the reactivity of electron deficient alkenes with organocopper(I) Lewis acid reagents

The synthesis of perhydrohistrionicotoxin is an example in which a ϒ-oxygenated α,β-unsaturated ketone undergoes efficient 1,4-addition with organocopper(I) Lewis acid reagents to produce a butyrated ketone. Ordinary organocopper(I) reagents such as (R_2CuLi) proved to be unsuccessful with this enone and formed undesired side products. Treatment of substrate **78** with reagents such as MeCu(CN)Li and Ph_2CuLi yielded none of the desired adducts. On the other hand, treatment of **78** with organocopper(I) Lewis acid reagent *n*-BuCu•$AlCl_3$ proceeds in a synthetically acceptable yield to give the expected 1,4-adducts.[68,69,70]

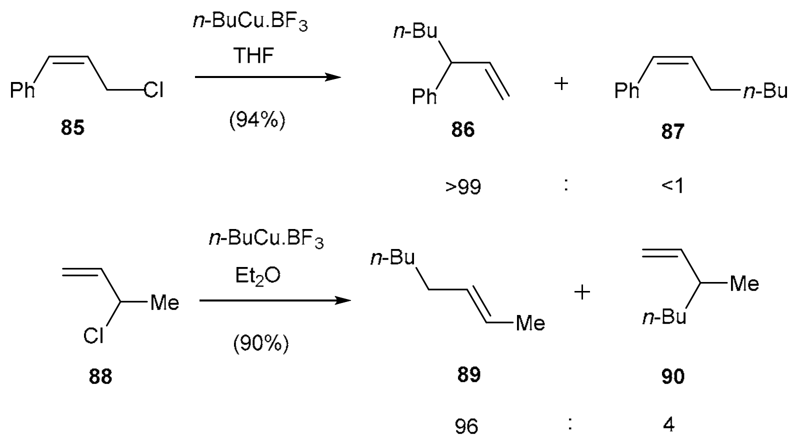


Scheme 18: Addition to α,β-unsaturated ketone

Reagent	Yield	Products ratio
MeCu(CN)Li	0 %	**79** 0:0 **80**
Ph_2CuLi	0 %	**83** 0:0 **84**
MeCu•$AlCl_3$	76%	**79** 92:8 **80**
n-BuCu•$AlCl_3$	77%	**81** 93:7 **82**
n-BuCu•BF_3	75%	**81** 100:0 **82**
PhCu•$AlCl_3$	69%	**83** 100:0 **84**

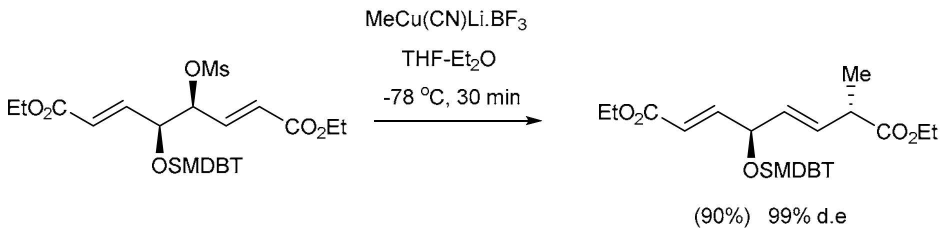
Table 2: Effect of different organocopper reagents on the enone 59

Organocopper Lewis acid complexes are the alkylating reagents of choice in S_N2' reactions with allylic substrates. As illustrated in Scheme 19 for the pair of allylic halides **85** and **88**, the butyl group is attacking the ϒ-position with a high regioselectivity and in excellent yield.[71]



Scheme 19: S_N2' Substitution reaction outcomes from allylic chlorides

(*E*)-ϒ-mesyloxy-α,β-enoates **91**, a promising intermediate derived from tartrates, reacts with organocyanocopper•BF_3 reagents providing a highly efficient synthesis of divinylmethanol derivatives. THF or mixed solvents involving THF are usually preferred so that completion of the reaction is achieved within a short period of time even at −78 °C.[72]



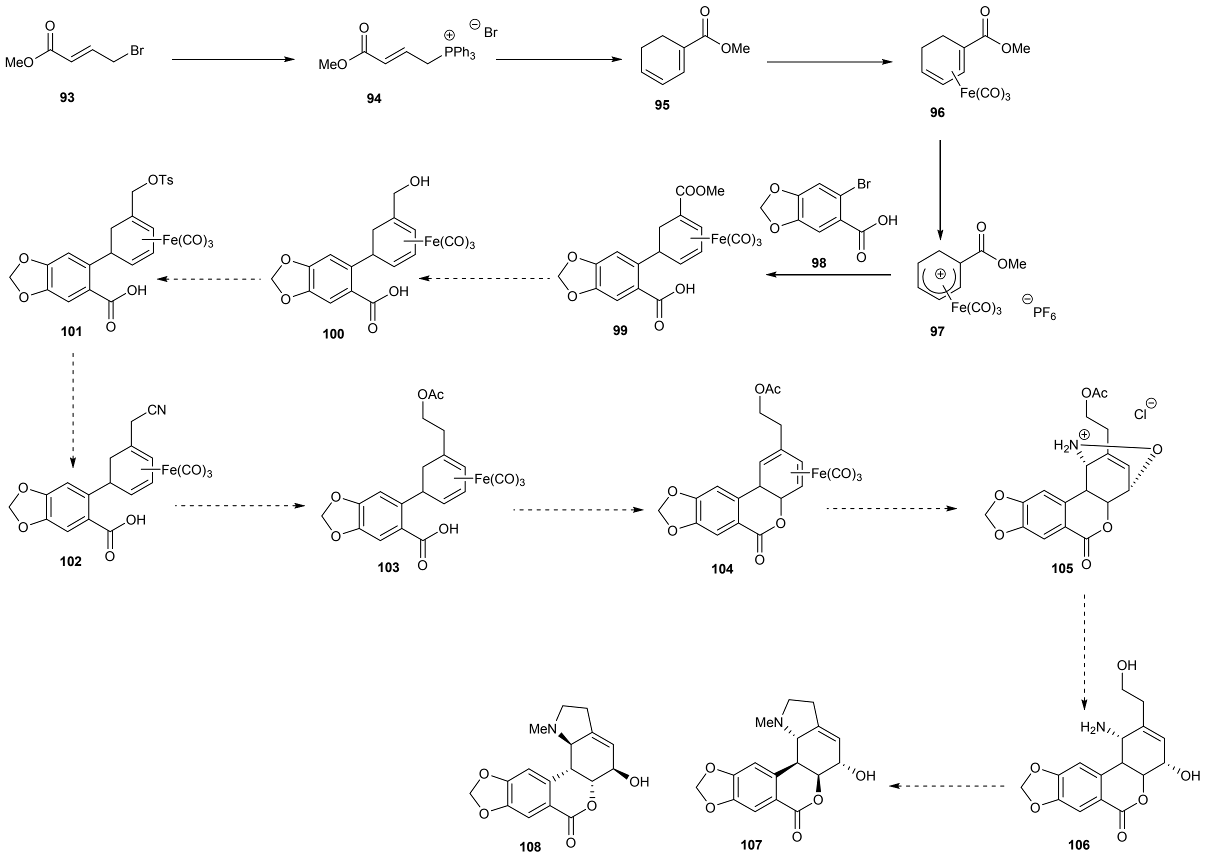
91 **92**

Scheme 20: Organocopper-Lewis acid complex in the (*E*)-stereoselective reaction of divinylmethanol derivatives

<u>Research Outline</u>

The aim of this project is to contribute to the design and implementation of an organoiron controlled stereoselective total synthesis of the alkaloid (+/−)-hippeastrine. Recent work within the Stephenson group has demonstrated that chiral alkaloids such as lycoramine and mesembrine can be obtained via arylation of a substituted cyclohehexadienyliron complexes, hence cyclohexadienyliron complexes are established as a potent stereocontrol electrophiles to address stereochemical issues encountered in other alkaloids synthetic methods.[27]

The subsequent arylation with a cyclohexadienyliron complex with an electron withdrawing group (-COOMe) was previously studied but still remains challenging. We seek synthetically to use such organometallic reagents in key steps in order to design new routes to related alkaloids show-casing the *1,2*-iterative strategy to complement the now well-established *1,1*-iterative approaches. Such a strategy should help us to obtain good regio-/ sterocontrol. The methods developed in the racemic series can later be employed with more advanced enantiomerically pure intermediates.



Scheme 21: Proposed synthetic route

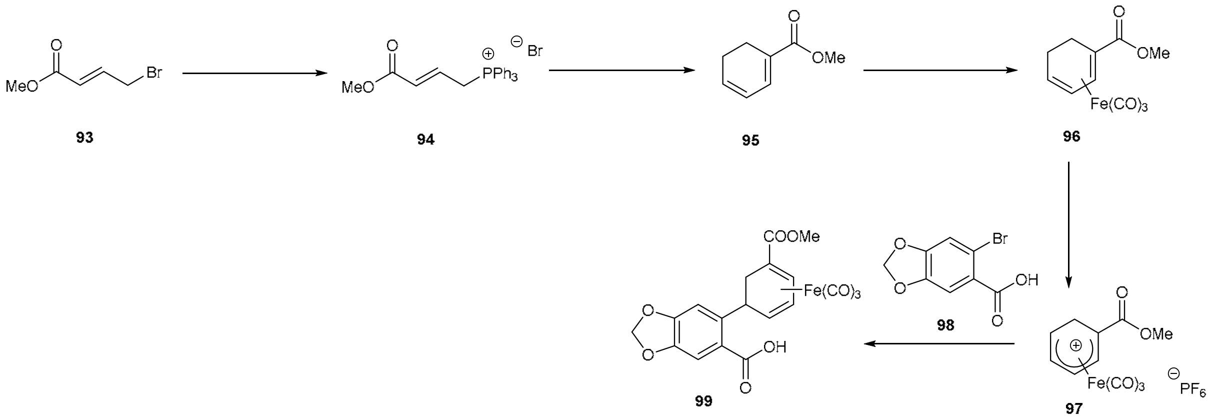
Scheme 21 shows how organoiron method used in the proposed synthetic route to (+/−)-hippeastrine (**107** and **108**). The plan for the synthesis starts with a convenient published[73] access route to the dienoic ester **95** by the formation of the Wittig salt, (3-methoxycarbonylallyl)-triphenylphosphonium bromide (**94**) followed by a tandem Wittig-Michael addition to obtain the cyclohexadiene methyl ester (**95**). This cyclohexadiene methyl ester (**95**) may then be treated with $Fe_2(CO)_9$ or a transfer reagent to produce the η^4 complex **96**. The next stage is the hydride abstraction of **96** with triphenylcarbenium hexafluorophosphate to form the highly electrophilic cation **97**. Treatment of the η^5 species **97** with the organocuprate formed from 6-bromopiperonylic acid (**98**) (by treatment with *n*-butyllithium and Cu(I)) produced **99**. The reaction should occur at the more reactive carbon site, reacting at the less hindered end of the π-system on the complex. Once produced, **99** goes through a series of functional group manipulations to install the two carbon side-chain needed later to build the D ring (see **Scheme 19** step **100** to **102**). Treatment of **103** with the aqueous base sodium hydrogen carbonate to produce, the carboxylate anion, cyclise by addition to the least hindered end of the cation π complex and form the B ring (**104**). The next stage in the synthesis would be an heterocycloaddition using a nitroso derivative in the presence of trimethylamine *N*-oxide. This step induces the removal of the η^4 tricarbonyliron group from **104** and produces the free diene **105**.[74] This step provides an efficient *cis*-selective method to introduce the C–N and C–O substituents on the C ring. The cycloaddition to be both regio- and diastereoselective. For the required diastereselectivity, nitroso group has to approach the diene from the opposite face of the lactone ring (ring B) either by steric control (addition on the unsubstituted side) or by precoordination to the iron (after loss of CO by oxidation with TMNO during decomplexation).[74] The N-O bond is then cleaved using aluminium amalgam strips to generate **106** before forming ring D. Reaction of **106** with the catalyst dihydridotetrakis(triphenylphosphine)ruthenium(II) would then finally provide our desired alkaloid (+/−)-hippeastrine (**107** and **108**).

2.Results and Discussion

2.1. Aims

This project aims to develop a pathway towards the synthesis of hippeastrine from the Wittig salt substrate. This will be achieved by completing the following steps:

1. Synthesis of the diene ester cation (**97**), starting from the phosphonium salt (**94**), followed by a tandem Wittig-Michael addition step, and then iron complexation and hydride abstraction to form the highly electrophilic cation.
2. Determination of the most appropriate organocopper and organolithium reagents and reaction conditions to form our desired building block (ABC ring) towards the synthesis of hippeastrine.

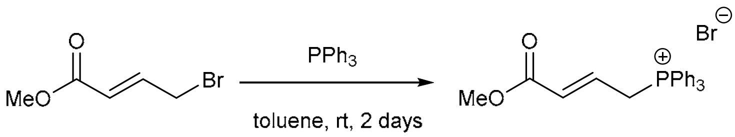


Scheme 22: Synthetic route towards the formation of a "building block"

2.2. Formation of cyclic diene

2.2.1. Synthesis of 3-ethoxycarbonylallyl-triphenylphosphonium bromide (**94**)

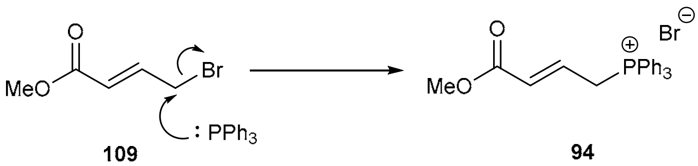
In order to begin to synthesise our first intermediate (**94**), we followed the procedure of Gradén *et al.*[73] (3-Methoxycarbonylallyl)-triphenylphosphonium bromide (**94**) was prepared by reacting triphenylphosphine with methyl 4-bromocrotonate **93** in toluene and the reaction was stirred for two days. The pure material was isolated as a white powder in 99% yield. Confirmation of the formation of the phosphonium salt was drawn from the ^{1}H NMR spectrum (the ^{1}H NMR spectrum showed a large aromatic area of fifteen protons that characterised the three benzene rings attached to the phosphorus atom and the characteristic singlet at 3.63 ppm. that corresponds to the methyl ester peak).



93 99 % 94

Scheme 23: Formation of 3-methoxycarbonylallyl-triphenylphosphonium bromide

A proposed mechanism is presented showing how the salt was formed from methyl 4-bromocrotonate and triphenylphospine through a nucleophilic substitution reaction (S_N2).

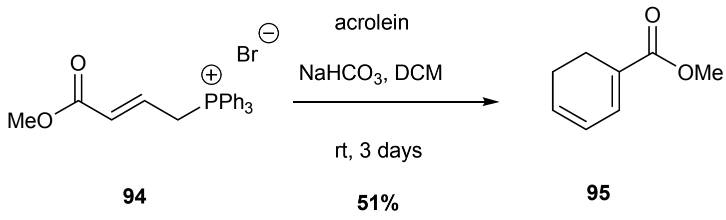


109 94

Scheme 24: Proposed mechanism for the formation 3-methoxycarbonylallyl-triphenylphosphonium bromide

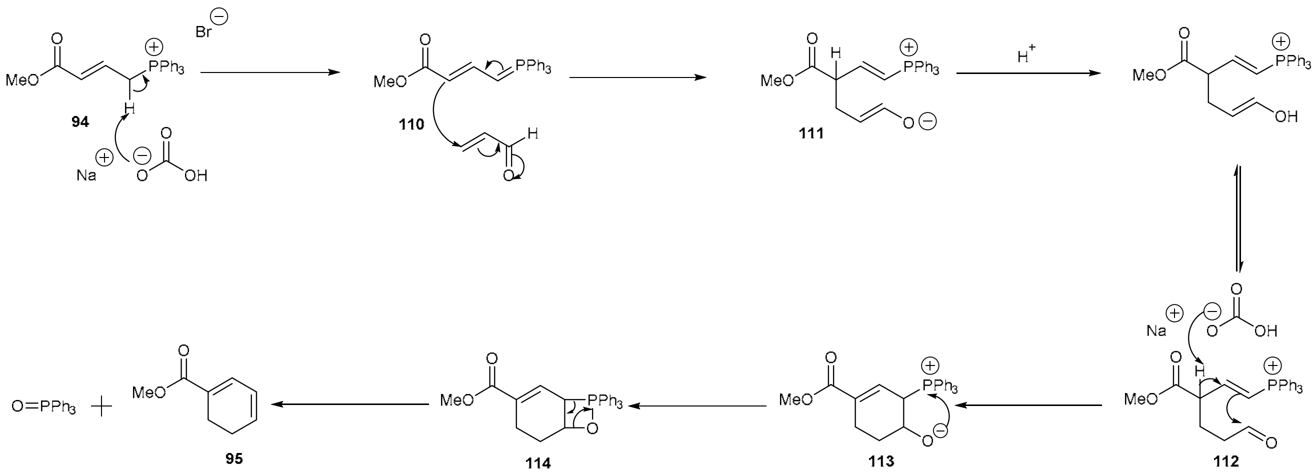
2.2.2 Synthesis of cyclohexa-1,3-dienecarboxylic acid methyl ester (**95**)

With our (3-methoxycarbonylallyl)-triphenylphosphonium bromide (**94**) in hand, we started the synthesis of the required cyclohexa-1,3-dienecarboxylic acid methyl ester (**95**) which is the backbone for the tricarbonyliron electrophile. A search of the literature revealed a protocol for the cyclisation of the diene methyl ester: treatment of (3-methoxycarbonylallyl-triphenylphosphonium bromide (**94**) with acrolein in the presence of saturated sodium bicarbonate and dichlomethane.[73] A colourless oil was obtained in 51 % yield. The yield obtained in this procedure is significantly less than the yield reported by Gradén's research group (83 %).[73] The ^{1}H NMR spectrum of **95**, however, fitted the one reported in the literature.[73]



Scheme 25: Formation of Cyclohexa-1,3-dienecarboxylic acid methyl ester

The first step of the reaction is initiated by a Michael addition by the Wittig reagent generated from (3-methoxycarbonylallyl)-triphenylphosphonium bromide (**94**). Sodium bicarbonate is used as the base to form the ylide which then reacts with acrolein to form the intermediate **111**. Tautomerisation of the enol ether leads to **112**. Deprotonation triggers an intramolecular Wittig reaction affording the desired fused cyclohexadiene methyl ester product **95**. In **114**, both the oxygen anion and the phosphonium cation are located at *cis* position, favouring the syn-elimination of triphenyl phosphine oxide. A detailed mechanism waits for further investigation. This is a concerted reaction as bonds are breaking and forming in a single step.



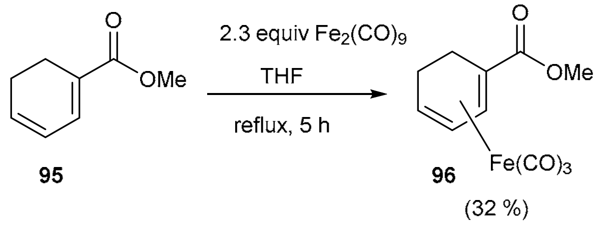
Scheme 26: Mechanism for the formation of cyclohexa-1,3-dienecarboxylic acid methyl ester

2.3. Tricarbonyliron complexation to cyclohexa-1,3-dienecarboxylic acid methyl ester (**96**)

2.3.1. Synthesis of η^4 methyl ester complex

The organoiron approach, discussed previously in the introduction, provides a valuable approach to functionalised cyclohexadiene systems. A review of the literature revealed a number of protocols for the formation of the methyl ester tricarbonyl complex.

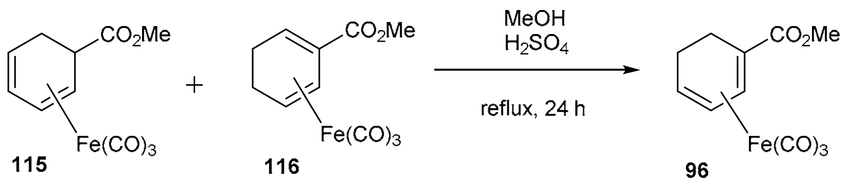
We opted to follow a modified synthetic route that Gradén *et al.*[73] used towards the synthesis of tricarbonyl(cyclohexa-1,3-dienecarboxylic acid)iron(0) to obtain our desired product. In order to obtain tricarbonyl(cyclohexa-1,3-dienecarboxylic acid methyl ester) iron (0), we first needed to reflux **95** with diironnonacarbonyl in THF. At 68°C, the temperature was high enough to affect the conjugation to the diene. The ease of synthesis and use of inexpensive reagents offset the disappointingly low yield. The progress of the reaction was monitored by IR spectroscopy, with the product having a pair of strong metal carbonyl bands at 2051 and 1975 cm^{-1}.



95 96

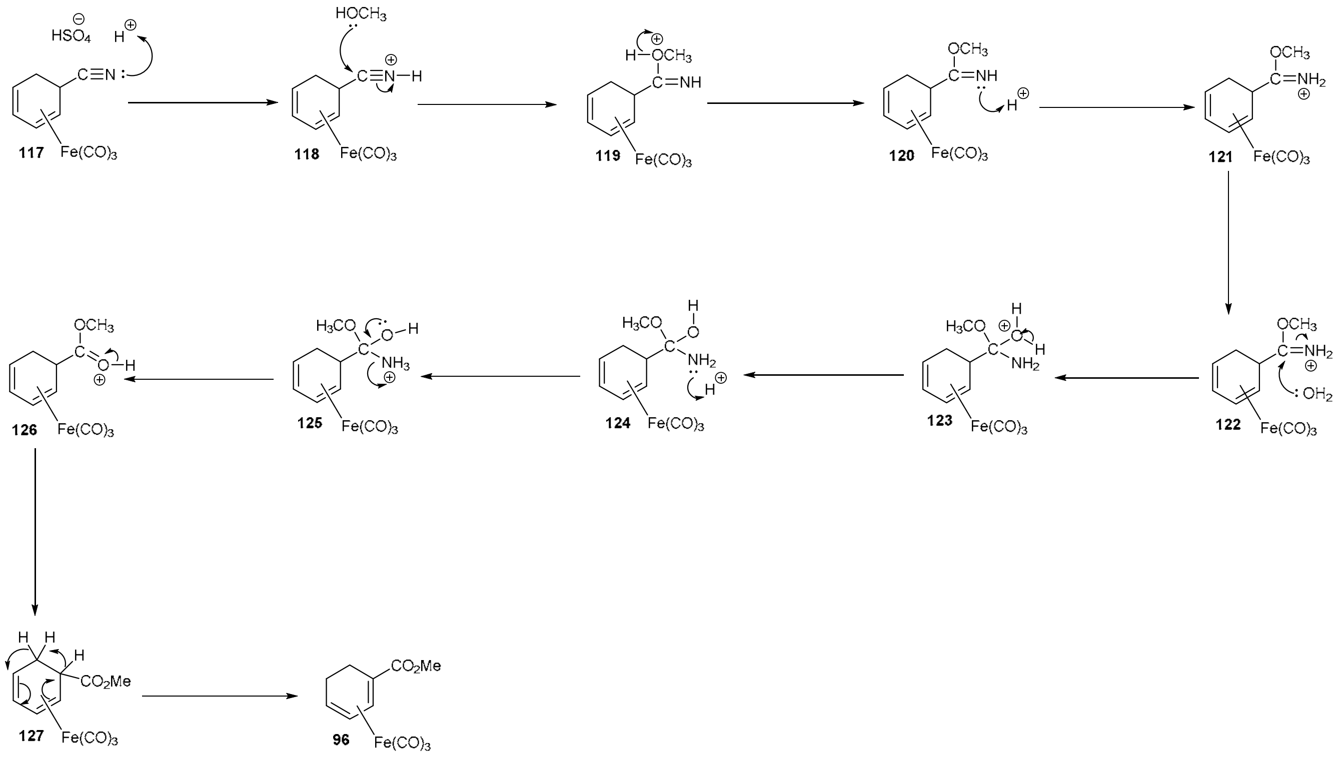
Scheme 27: Formation of tricarbonyl (cyclohexa-1,3-dienecarboxylic acid methyl ester)iron(0)

However, other approaches described in the literature were also examined. For example one method uses the isomerisation of the complexes, tricarbonyl -2-methoxycarbonylcyclohexa-1,3-dieneiron (**115**) and tricarbonyl-5-methoxycarbonylcyclohexa-1,3-dieneiron (**116**) to form our desired product **96** (**Scheme 28**). The mixture of complexes was refluxed for 24 hours in methanol containing sulfuric acid, followed by a diethyl ether and ice water work-up.[75] The only major issue in this reaction is the preparation of isomers, which is lengthy and expensive, hence we chose not to follow this route.



Scheme 28: Formation of tricarbonyl (cyclohexa-1,3-dienecarboxylic acid methyl ester)iron(0) through isomerisation of a set of complex

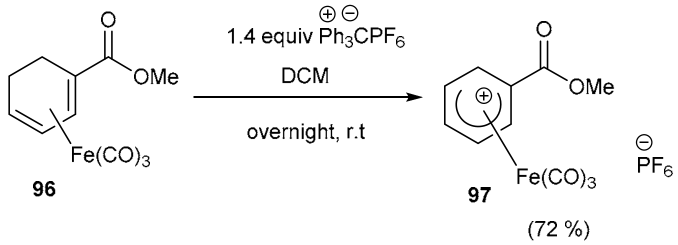
Another approach which has been reported in the literature is the acidic methanolysis of tricarbonyl-5-cyanocarbonylcyclohexa-1,3-dieneiron. Arthur J. Birch *et al.*[76] used a procedure in which the nitrile complex **117** was treated in the same way as the method discussed previously. This procedure has been shown to be very effective; excellent yields was obtained (*i.e.* 80 %).[76] The proposed mechanism of the reaction is illustrated below (**Scheme 29**). The mechanism is initiated by protonation of the nitrile, followed by a nucleophilic addition of methanol, subsequent acidic hydrolysis of **121** leads to the formation of **127** and a final isomerisation gives desired **96**.



Scheme 29: Proposed mechanism for the formation of tricarbonyl (cyclohexa-1,3-dienecarboxylic acid methyl ester)iron(0) using the starting material tricarbonyl-5-cyanocarbonylcyclohexa-1,3-dieneiron

2.3.2 Formation of the η^5 salt

The next step was the formation of the tricarbonyliron cation **97** by hydride abstraction using the condition described by Fischer.[77] Treatment of **96** with triphenylcarbenium hexafluoropshate ($Ph_3C^+PF_6^-$) in dichloromethane at room temperature overnight resulted in the formation of the cation with a hexafluorophosphate counter anion (**Scheme 30**).



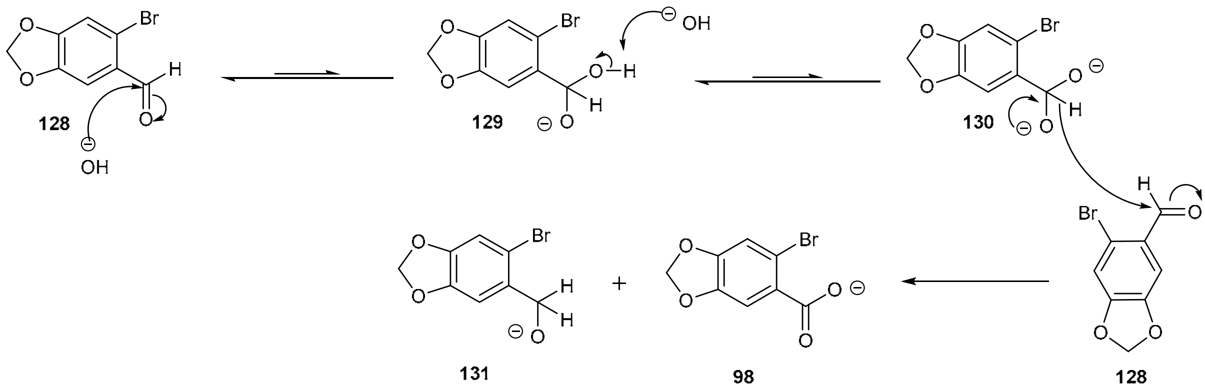
Scheme 30: Formation of Tricarbonyl(η^5-carboxylic acid methyl ester) iron (1+) hexafluorophosphate (1-)

Cyclohexa-1,3-dienecarboxylic acid methyl ester gives **97** as the only isolatable product. Due to the steric demand of the methyl ester group, the hydrogen atom at the 5-position is the less hindered hence hydride abstraction will be favoured at this position.[78]

2.4. Preparation of 6-bromopiperonylic acid

2.4.1. Canizzaro reaction

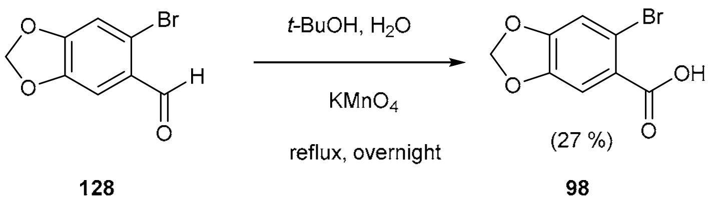
6-Bromopiperonylic acid (**98**) is readily available from chemical suppliers but unfortunately it is costly. A search in the literature provided a few different routes. Fales *et al*. was the first procedure that we considered for the synthesis of 6-bromopiperonylic acid (**98**). The method is based on the Cannizzaro reaction of 6-bromopiperonal (**128**).[79] Unfortunately the reaction did not work; neither of the two compounds were recovered which was indicated by ^{1}H NMR spectroscopy. Moreover, considering that a Cannizarro reaction would give at best a 50% yield, we moved on without further studying this reaction.



Scheme 31: Mechanism of the Cannizzaro reaction of 6-bromopiperonal

2.4.2 $KMnO_4$ oxidation

Another approach which has received large attention to afford 6-bromopiperonal[80] is the oxidation of 6-bromopiperonal using potassium permanganate.



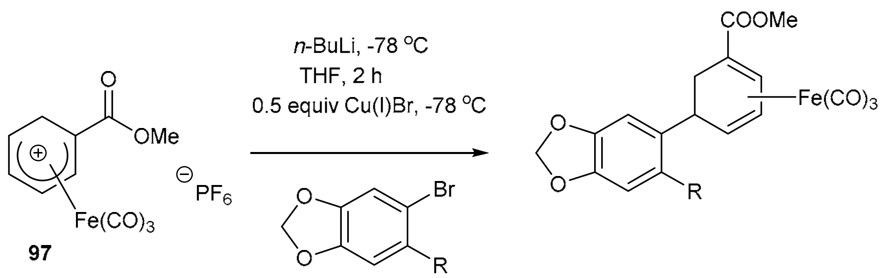
Scheme 32: Formation of 6-bromopiperonylic acid

In this case, we were rewarded with success. The ^{1}H NMR spectrum of the product obtained matched the one reported in literature.[80] Methylene protons were observed at 6.15 ppm. (lit. 6.07 ppm.), the two protons on the phenyl ring were observed at 7.29 ppm. for the one adjacent to the bromine unit and 7.31 p.p.m. for the one adjacent to the carboxylic acid group (lit. 7.34 and 7.54 ppm.). The carboxylic acid proton was observed at 13.14 ppm. (lit. 11.0 ppm.). The final product is highly hygroscopic and it was kept in a desiccator filled with phosphorus pentoxide as dehydrating agent.

2.5. Aryl addition to tricarbonyl(η^5-carboxylic acid methyl ester) iron (1+) hexafluorophosphate(1−)

Nucleophilic addition to cationic (cyclohexadienyl) iron complexes is well established and previous studies within the Stephenson group have found a route to hippeastrine using organocuprate reagents.[81] **Scheme 33** illustrates the addition of 6-bromopiperonylic derivatives **98**, **132**, **133** (using copper(I) bromide and an aryllithium reagent) to the η^5 salt

97. The nucleophile is generated by the addition of *n*-butyllithium (two equivalents were needed for the compound **98** and 1.2 equivalents were needed for compounds **132** and **133**) followed by the addition half of an equivalent amount of the copper(I) bromide. The reaction was cooled down to a temperature of -78 °C and left to stir for two hours. Once the organocuprate was formed, the η^5 salt **97** was added in a single portion. The reaction mixture instantaneously changed colour.



98 R= CO_2H **99** R= CO_2H

132 R= H **134** R= H

133 R= CH_2OTHP **135** R= CH_2OTHP

Scheme 33: General preparation method for the addition of nucleophiles to cationic (cyclohexadienyl)iron complex

Several attempts to generate compound **99** using the methodology presented in **scheme 33** were made. Formation of nucleophile **98** was attempted, using *n*-butyllithium for the transmetallation, followed by addition of half of an equivalent of copper(I) bromide. However, upon addition of the salt, no trace of the expected product was observed. Discussion of this issue will be presented in the following paragraphs. Copper(I) bromide is highly hygroscopic which could have caused problems in the reaction but remained our preferred reagent compared to copper(I) cyanide that is more toxic. Metalation at the *ortho*-position of arylcarboxylic acid can be achieved because of additional activation provided by the methylenedioxy moiety, therefore the deprotonation of this position could lead to the formation of by-products.

As explained previously the nucleophilic addition of the salt to 6-bromopiperonylic acid raised few issues. The lack of product could be due to:

1. Presence of water in 6-bromopiperonylic acid which was interfering with the lithiation process.

2. Problem with the deprotonation / lithium halogen exchange
3. Problem in the organocuprate formation

To avoid wasting tricarbonyl(η^5-carboxylic acid methyl ester)iron(1+) hexafluorophosphate, we used deuterium oxide (D_2O) as the electrophile to investigate the metalation problem encountered with 6-bromopiperonylic acid before the addition of the η^5 salt.

2.5.1. Metalation and deuteration of 2-bromobenzoic acid

We started with the simple 2-bromobenzoic to investigate the lithium-halogen exchange followed by deuteration process. Once the reaction was fully completed, its ^{1}H NMR spectrum was obtained and compared with 2-bromobenzoic acid and the simple benzoic acid to determine the percentage of deuterium incorporation at the *ortho*-position of benzoic acid. The first method implied the addition of *n*-butyllithium to a solution of 2-bromobenzoic acid in THF at −78 °C. The reaction was left to stir at −78 °C for two hours followed by an addition of D_2O (10 equivalents). The reaction was then finally quenched with 1M HCl and the aqueous phase was extracted with dichloromethane (this is to ensure that none of the compounds formed in the reaction are obtained as salts which would affect the NMR and would prevent the comparison with SM and simple dehalogenated compound).

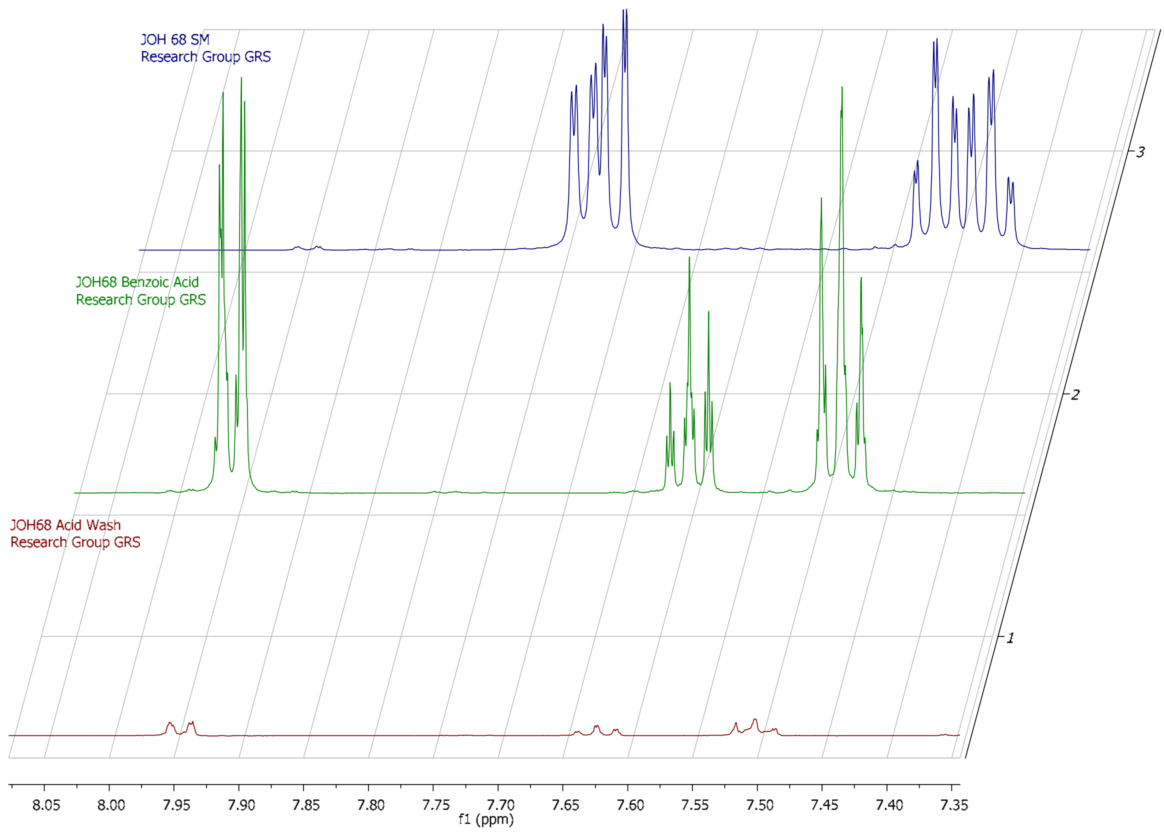


Figure 8: ^{1}H NMR stack of deuterated benzoic acid, 2-bromobenzoic acid and benzoic acid

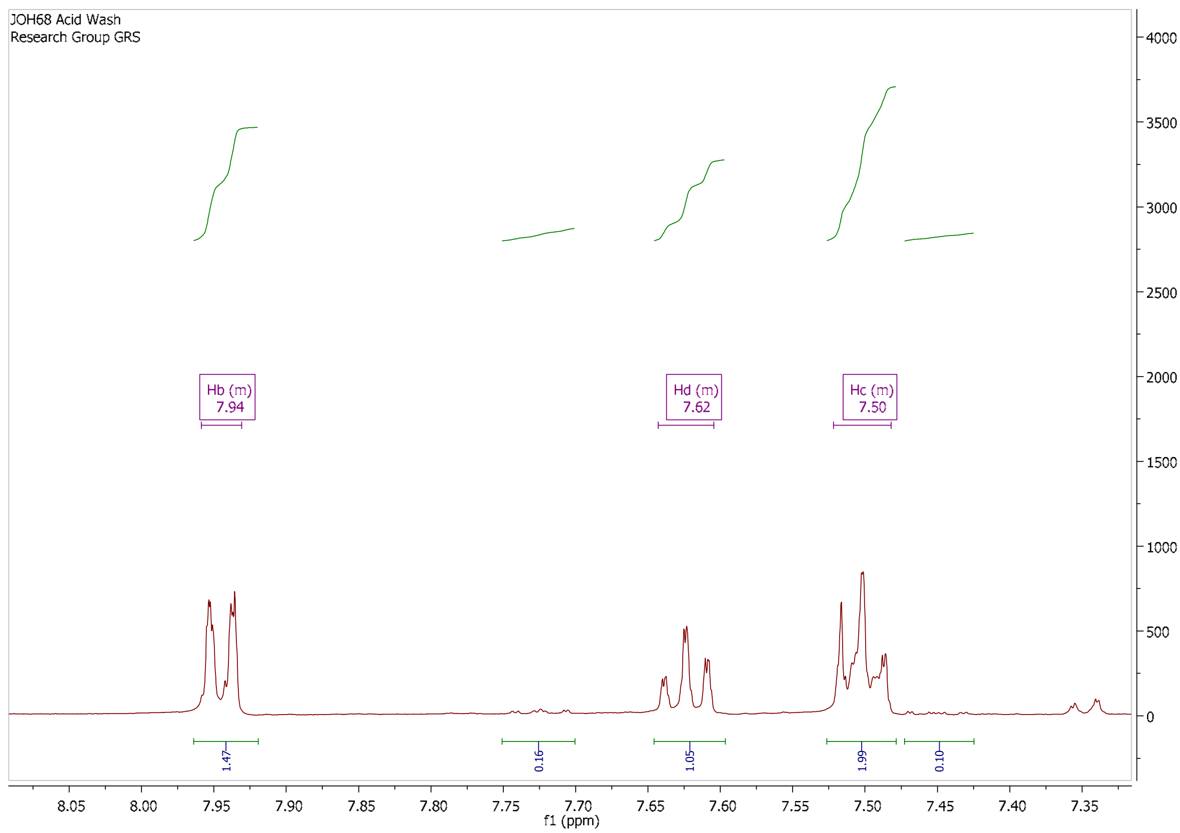
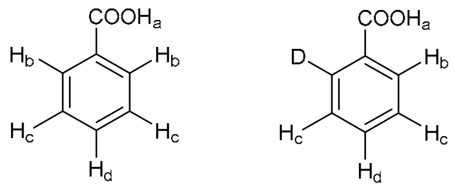


Figure 9: ^{1}H NMR of deuterated benzoic acid in method 1



136 **137**

Figure 10: Benzoic acid and deuterated 2-bromobenzoic acid protons labelling

This stack of ^{1}H NMR (**Figure 8**) shows the comparison of the deuterated product **137** (red) with the starting material 2-bromobenzoic acid (blue) and benzoic acid (**136**, this would be the product obtained by quench of the lithiobenzene derivative by a proton source, see **Figure 8** in green) in the region of interest (from 7.35 ppm to 8.05ppm). It can be observed (**Figure 9**) that 7% of the starting material is present in the product (0.16/(0.16 +1.99)= 0.07= 7% of starting material). H_c is present in both **136** and **137**, therefore it can be used as a reference, and the integration of H_c from **136** and **137** has been set as 2 in **Figure 9** acid wash spectrum. The difference of the integral of our "reference" protons H_c with the integral of proton H_b allowed us to obtain the percentage of deuterium incorporation. In this method the integral of H_c is equal to two and the integral of H_b is 1.47 (2.00 −1.47 = 0.53). By this method we calculated a 53% incorporation of deuterium. If we neglect the 7% of 2-bromobenzoic acid remaining in this reaction, 47% of benzoic acid was obtained from lithiated 2-bromo benzoic acid which means there was a significant proton source in this reaction mixture. We thought that perhaps, the bromine-lithium exchange could be faster than the deprotonation of the carboxylic acid (which could sound surprising considering the low p*K*a of benzoic acid) which would explain the large proton incorporation. To test this idea we moved on to another substrate, 5-methoxy-2-bromobenzoic acid, which would be a better model for the expensive/precious 2-bromopiperonylic acid.

	Method 1
Deuterated benzoic acid	53 %
Benzoic acid	47 %

Table 3: Percentage deuterium incorporation and side product present in each method

2.5.2. Metalation and deuteration of 5-methoxy-2-bromobenzoic acid

5-Methoxy-2-bromobenzoic acid was lithiated and deuterated. Method 2 involved the addition of LiHMDS at 0 °C over a ten minutes period followed by the addition of *n*-butyllithium at −78 °C and the reaction was stirred for two hours at this temperature and was quenched with D_2O. In method 3, NaH was added to the starting material at −78 °C and was warmed up at room temperature. The reaction was cooled back to −78 °C at which point *n*-butyllithium was added and the reaction was stirred for one hour and then quenched with D_2O. In method 4, methyllithium was added to the starting material at −78 °C and the reaction was warmed up to −40 °C. The reaction was cooled back to −78 °C followed by the addition of *n*-butyllithium, after which the reaction was stirred for one hour and was quenched with D_2O. For every reaction completed, the ^1H NMR spectrum of the crude product was compared with the ones of 5-methoxy-2-bromobenzoic acid and 3-methoxybenzoic acid to determine the percentage of deuterium incorporation in each reaction.

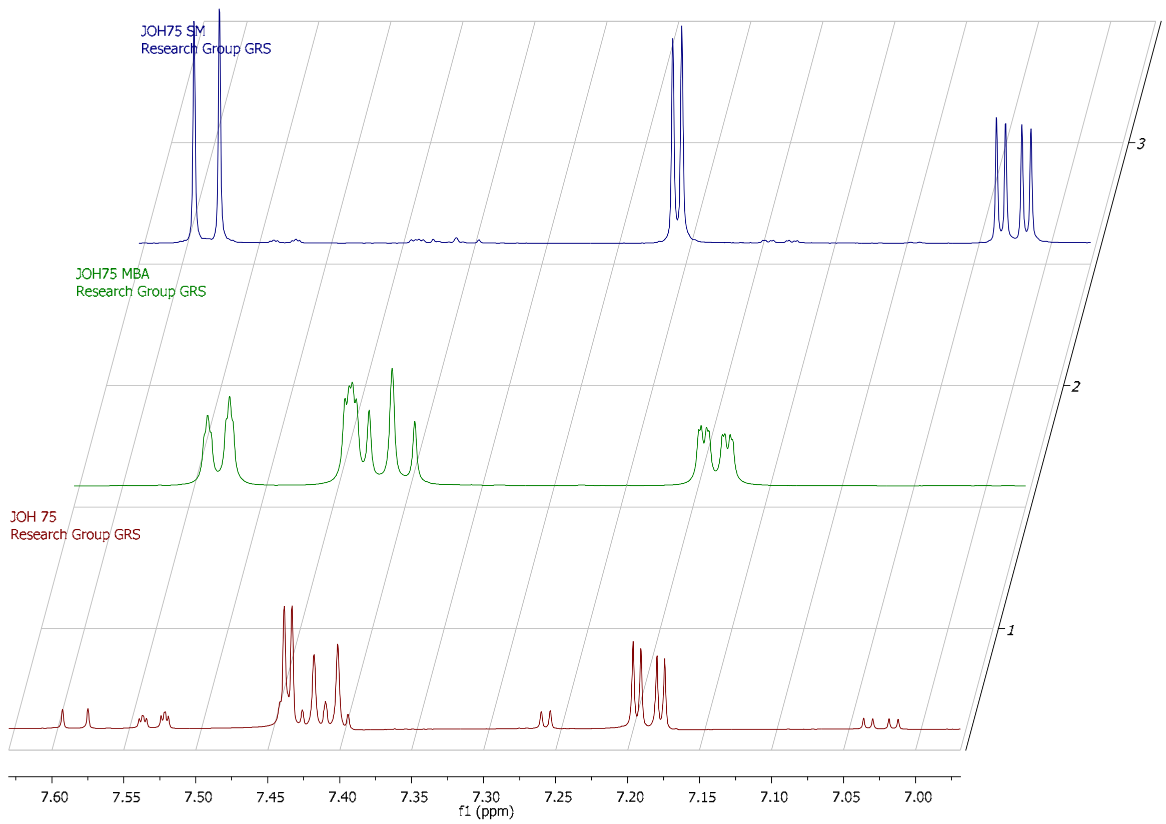


Figure 21: ^1H NMR stack of deuterated 3-methoxybenzoic acid,5-methoxy-2-bromobenzoic acid and 3-methoxybenzoic acid using Method 2

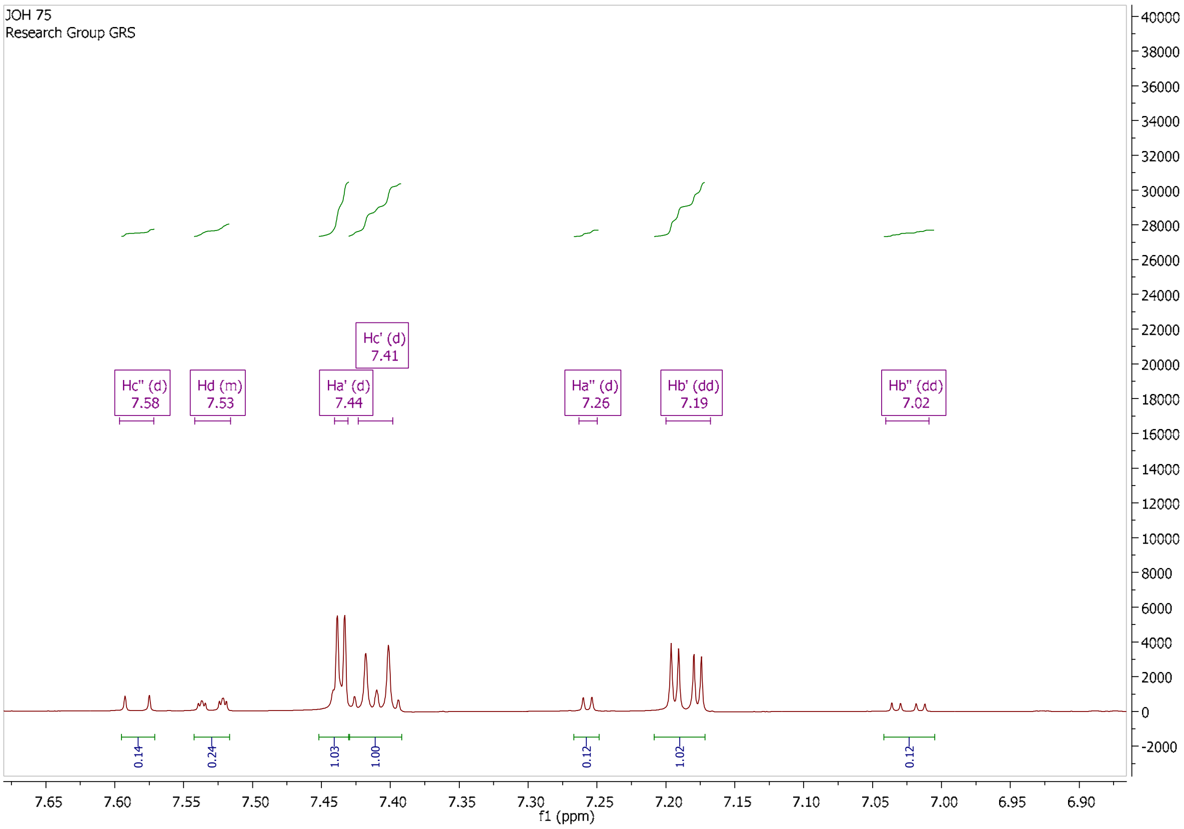
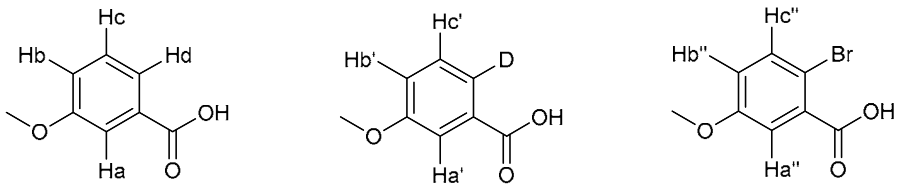


Figure 12: ^{1}H NMR for lithiated and deuterated 3-methoxybenzoic acid in the region of interest



138 **139** **140**

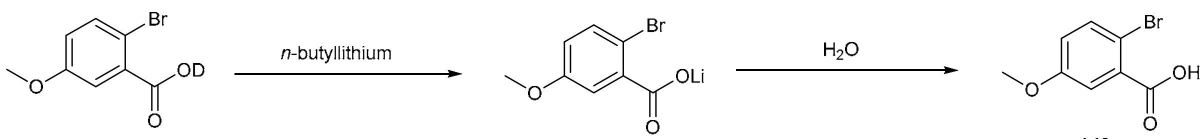
Figure 13: 3-methoxybenzoic acid and deuterated 3-methoxybromobenzoic acid protons labelling

Figure 11 shows the ^{1}H NMR of our lithiated and deuterated product **139** in method 2(red) with the starting material 5-methoxy-2-bromobenzoic acid **140** (blue) and 3-methoxybenzoic acid **138** (green) of the region of interest (from 7.00 ppm to 7.60 ppm). To obtain our percentage deuteration, we know the integral of H_a + H_a' to 1 (at 7.44 ppm). Then we subtract from this the integration corresponding to proton H_d present in the 3-methoxybenzoic acid (multiplet between 7.55-7.52 ppm) which integrates with a value of 0.24 therefore 1-0.24= 0.76 meaning 76% of deuterium incorporation if we neglect the starting material. Integration of the doublet at 7.26 ppm (starting material) gave 11% SM (0.12/1.12) . Overall we have 11% SM, 21% (0.24/1.12= 0.21) of 3-methoxybenzoic acid and finally 68% (0.76/1.12= 0.68) of the deuterated product **139**. The same method was used to calculate the deuteration percentage in each reaction (see Experimental section for a full reaction method).

	Method 2	Method 3	Method 3	Method 4
5-methoxy-2-bromobenzoic acid	11 %	33 %	16 %	71 %
3-methoxybenzoic acid	21 %	37 %	13 %	26 %
Deuterated 3-methoxybenzoic acid	68 %	28 %	71 %	3 %

Table 4: Percentage of deuterium incorporation and side product present in each method

Overall, **Table 4** is showing positive results for method 2 and 3. This is probably showing us that the proton of the carboxylic acid was quenching the reaction.



Scheme 34: Lithiation and quenching of deuterated 3-methoxybenzoic acid

Scheme 34 is a proposed experiment that would prove that when using *n*-butyllithium, the bromine-lithium exchange is faster than the deprotonation of the carboxylic acid, which would then quench the reaction.

2.5.3. Metalation and deuteration of 6-bromopiperonylic acid

In order to save the precious 6-bromopiperonylic acid, we performed the deuterium quench experiment to optimise the reaction.

6-Bromopiperonylic acid was lithiated and deuterated. Method 5 employed two equivalents of *n*-butyllithium at −100 °C. The reaction was stirred for one hour followed by the addition of D_2O at −100 °C. In Method 6, 1.2 equivalents of LiHMDS were added to the starting material **98** over a period of ten minutes (see Experimental section for more time details) followed by the addition of *n*-butyllithium. The reactions were stirred for different times and were quenched with deuterium oxide. Method 7 involved the addition of NaH to 6-Bromopiperonylic acid (**98**) at −78 °C and then reactions were allowed to warm to room temperature for thirty minutes. This was followed by the addition of *n*-butyllithium at −78 °C and reactions were stirred at various times (see Experimental section for time details) and were quenched with D_2O. In method 8, methyllithium was added to the starting material **98** at −78 °C and the reaction was warmed to −40 °C. The reaction was cooled back to −78 °C followed by the addition of *n*-butyllithium and the reaction was then stirred for one hour and was quenched with D_2O.

For every reaction completed, the ^{1}H NMR of the reaction was compared with those of 6-Bromopiperonylic acid and piperonylic acid to determine the percentage of deuterium incorporation in each reaction.

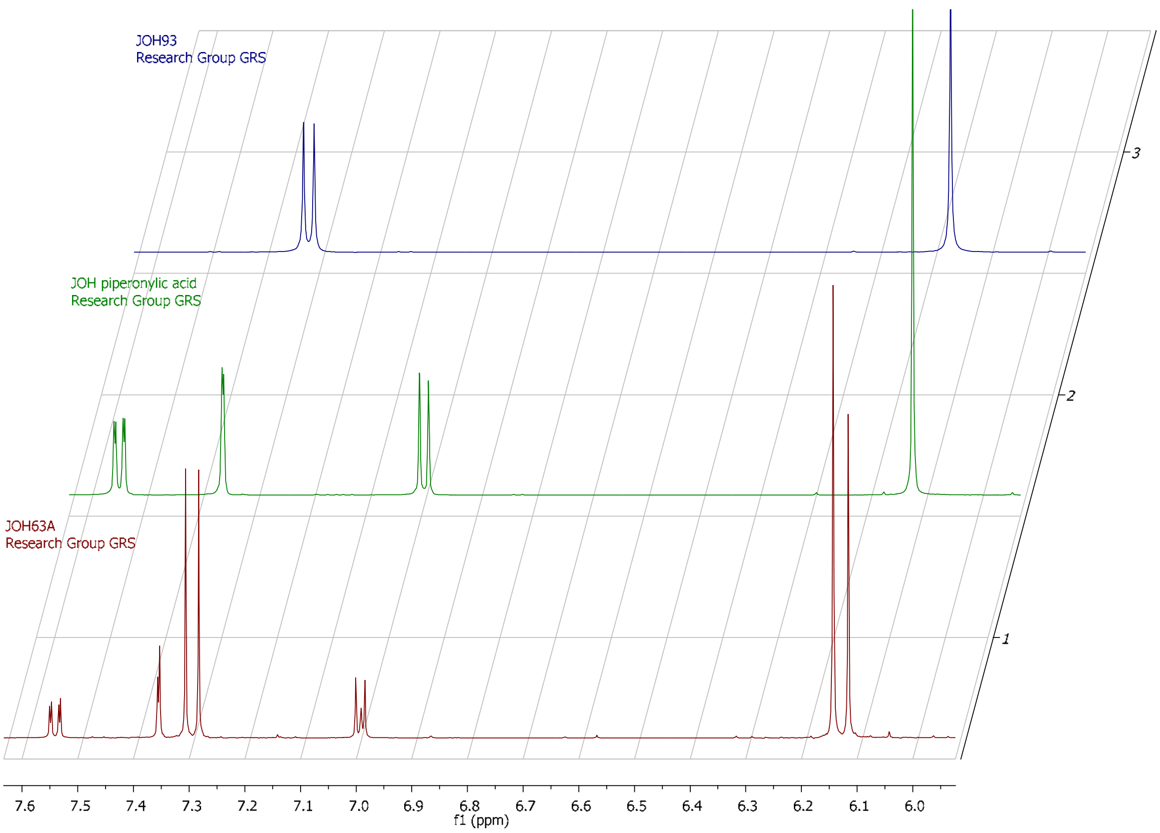
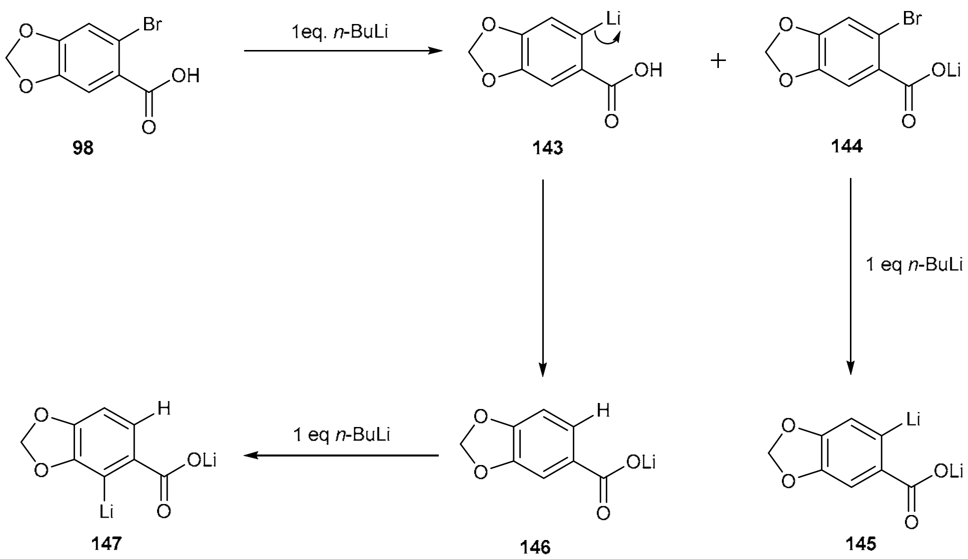


Figure 14: ^{1}H NMR stack of deuterated piperonylic acid, 6 -bromopiperonylic acid and piperonylic acid using method 5

Figure 14 shows a stack of ^{1}H NMR that compare our lithiated and deuterated product **149** (red) with the starting material 6-bromopiperonylic acid **98** (blue) piperonylic acid **148** (green) in the region of interest (from 6.85 ppm to 7.65 ppm) using method 5. It can be observed that a mixture of different compounds is present in the product. Other than starting material **98**, piperonylic acid and our deuterated product, another outcome was observed in our ^{1}H NMR. Deuteration also happened at the 2-position **150** (**Figure 16**) that is due to addition of one equivalent of *n*-butyllithium hence exchanging bromine for lithium. The lithium is exchanged for the acidic proton which then after addition of the second equivalent of *n*-butyllithium deprotonate and lithiate at the 2-position



Scheme 35: Possible lithiation position after addition of two equivalent of *n*-butyllithium

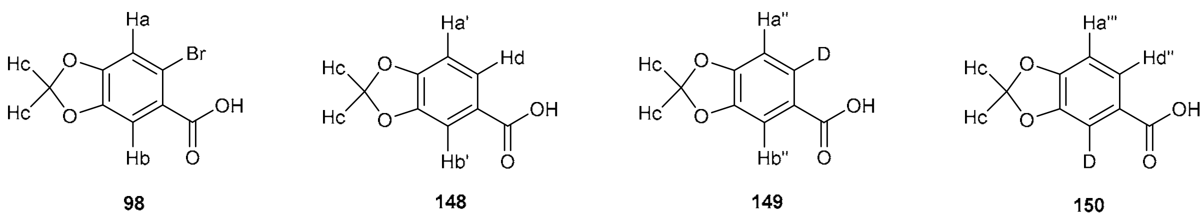


Figure 16: protons labelling of the different outcomes obtained in the lithiation and deuteration process of 6-bromopiperonylic acid

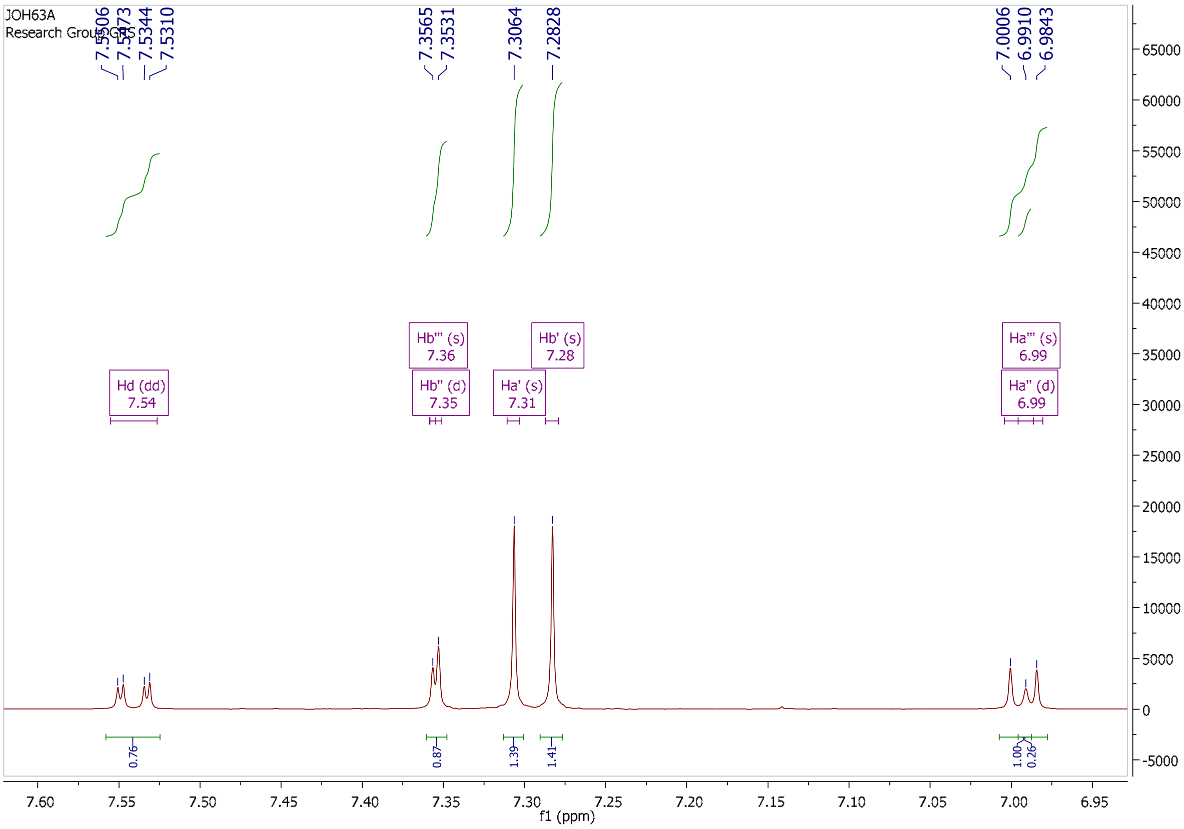


Figure 17: Deuteriation experiment of 95 using method 5: aromatic region of the ^{1}H NMR spectrum

The proton NMR spectrum shows a mixture of products **95**, **148** and **149** and **150**. In order to calculate the percentage deuteriation (we will first omit the SM), we will use the only proton not affected by the lithiation being Ha (signal at 6.99 ppm) as our reference and set its integral to 1. The integration of the signal at 7.54 ppm (0.76) gives us the percentage deuteriation at the d position (**149**, 24%), and the integral of the signal at 7.35 ppm (0.87) gives us the percentage deuteriation at the b position (**150**, 13%). When we account for the presence of unreacted starting material (Ha' and Hb' both individually integrate for 1.4), we obtain the following proportions: 58% of **98** [1.4/(1.4+1) = 0.58], 26% of **148** [(1-0.13-0.24)/(1+1.4) = 0.26), 10% of **149** [0.24/(1+1.4) = 0.10] and 5% of **150** [0.13/(1+1.4) = 0.05]. The same reasoning was used to acquire percentage deuteriation using other methods. (see Experimental section)

Method 6	Entry 3	Entry 4	Entry 5	Entry 6
95	5 %	1 %	6%	26 %
147	30 %	44 %	28 %	8 %
148	41 %	16 %	15 %	10 %
146	24 %	39 %	51 %	54 %

Table 5: Percentage of deuterium incorporation and side product present in method 6

Table 5 is showing different entries. Entries 3 and 4 are different attempts using the same conditions. Entry 5 exhibits different conditions, after addition of LiHMDS, the reaction was stirred at −78 °C for two hours and then warmed up at 0 °C for thirty minutes. The reaction was cooled back to −78 °C and *n*-butyllithium was added and the reaction was stirred for two hours at −78 °C and then quenched with HCl followed by D_2O. Entry 6 used different conditions to entries 1,2 and 3, after addition of LiHMDS, the reaction was stirred at −78 °C for one hour and then warmed up at 0 °C for thirty minutes. The reaction was cooled back to −78 °C and *n*-butyllithium was added and reaction was stirred for one hour at −78 °C. The reaction was quenched with HCl followed by D_2O. (see experimental section for details).

Method 7	Entry 7	Entry 8	Entry 9
95	72 %	91 %	31 %
147	22 %	5 %	3 %
148	2 %	1 %	12 %
146	4 %	2 %	53 %

Table 6 : Percentage of deuterium incorporation and side product present in method 7

Table 6 is showing different entries. Entries 7 and 8 are different attempts using the same conditions. Entry 9 exhibits different conditions from entries 7 and 8, after addition of NaH, the reaction was stirred at −78 °C and then warmed to room temperature. The reaction was cooled back to −78 °C and *n*-butyllithium was added and reaction was stirred for ten minutes at −78 °C. This was followed by a temperature rise and the reaction was stirred between −40 to −20 ˚C for one hour and half. The reaction was quenched with HCl followed by the addition of D_2O.

Method 8	Entry 10	Entry 11
95	16 %	35 %
147	47 %	19 %
148	3 %	33 %
146	33 %	12 %

Table 7: Percentage of deuterium incorporation and side product present in method 4

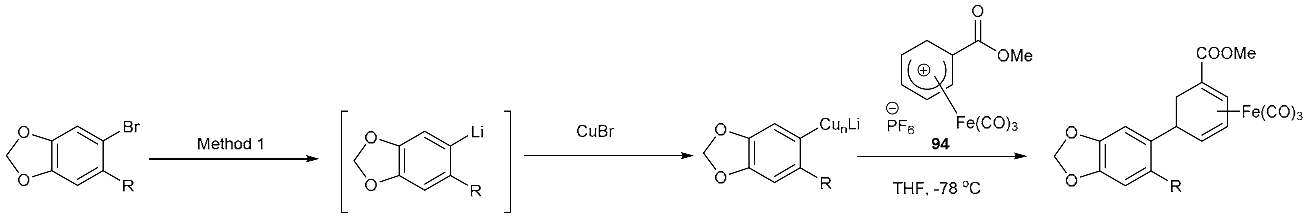
Table 7 is showing different entries. Both entries are using same temperature conditions but the time that the reaction was left to stir after the addition of methyllithium is altered. (see experimental section for details).

Conclusion for the deuteration experiments:

All these deuteriation experiments showed that either method 2, method 4 and method 6 were the best, giving at best 47 % deuteriation using **98**, but also 68 % deuteriation using **140**. When omitting the recovered starting materials (**98** or **140**), the best percentage deuteriation were obtained using method 2.

2.6. Arylation results using improved method for the metalation of arylbromide starting materials

Considering the results previously obtained in the deuteration experiments, we chose to use method 1 (a Schlenk line was used this time during the entire reaction process, flushing nitrogen gas) to form the lithium salt. This lithium salt would then be transformed to a cuprate using the method of Stephenson[82] which would then be reacted with cation **97** (**Scheme 36**). The results of the arylations are shown in Table **8** and are described below.



98 R= CO_2H
132 R= H
133 R= CH_2OTHP

99 R= CO_2H
134 R= H
135 R= CH_2OTHP

Scheme 36: Improved arylation reaction

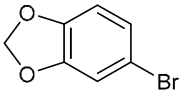
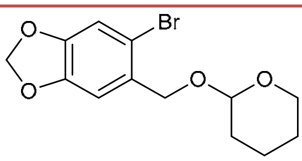
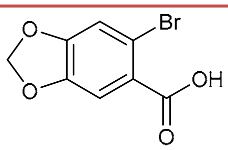
Ar	Product	Yield (%)
	**134**	19
	**135**	0
	**99**	27

Table 8: Arylation results

Reaction of tricarbonyl(η^5-carboxylic acid methyl ester)iron(1+) hexafluorophosphate (**97**) with the cuprate salt of 4-bromo-1,2(methylenedioxy)benzene (**132**) at −78 °C , gave a dark yellow oil. Chromatography on silica removed any impurities to give the pure tricarbonyl [η^4-1-methyl ester-5-(3',4'-methylenedioxy)phenylcyclohexa-1,3-diene]iron(0) (**134**) in 19% yield as a brown-yellow oil. The yield was disappointing but would most likely have been improved by repeating the reaction more carefully, which was however not possible due to the lack of time.

Another arylation using compound **133** that presents a bulkier R substituent (which was prepared in two steps). First, 3,4-methylenedioxybenzyl alcohol was brominated with *N*-

bromosuccinimide giving 2-bromo-4,5-ethylenedioxybenzyl alcohol (**151**) as a white solid (95 % yield). This product reacted with pyridinium *p*-toluenesulfonate and 3,4-dihydro-2*H*-pyran affording 2-bromo-4,5-methylenedioxybenzyl 1-tetrahydropyranyl ether (**152**)[83] in 89% yield. From **133**, the organocuprate nucleophile was prepared using method 1 for the lithiation and then adding copper(I) bromide; tricarbonyl(η^5-carboxylic acid methyl ester)iron(1+) hexafluorophosphate was added to the nucleophile. However chromatographic purification proved to be difficult and the different fractions recovered were evaporated. ^{1}H NMR of these fractions were performed in chloroform and no recognisable proton signals are present that is inexplicable to us.

Finally, tricarbonyl[η^4-1-methyl ester-5-(3',4'-methylenedioxy-6'-carboxyphenyl)cyclohexa-1,3-diene]iron(0) (**99**) was obtained in 27% yield from **98** and **97** using method 1 for the lithiation. The proton NMR of **99** was complex due to the presence of diastereoisomers which complicates the ^{1}H NMR spectrum by doubling resonances. The methoxy signal is the simplest still significant example that can be used to explain this phenomenon. Indeed, at 3.72 ppm, two peaks are present which integrate three protons for each peak.

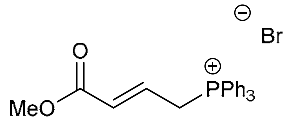
Conclusion

In summary, we have successfully synthesised tricarbonyliron cation **97** in 72% yield. We also investigated the metalation problem encountered with 6-bromopiperonylic acid (**98**) and the η^5 salt by using deuterium oxide as an electrophile with **98** and compounds with similar physical properties (2-bromobenzoic acid and 5-methoxy-2-bromobenzoic acid. Our desired tricarbonyl[η^4-1-methyl ester-5-(3',4'-methylenedioxy-6'-carboxyphenyl)cyclohexa-1,3-diene]iron(0) (**99**) was successfully synthesised in 27% yield using method 1. Compound **132** and **133** underwent metalation with the tricarbonyliron cation **97** to give **134** and **135** in 19% and 0% yield respectively. The synthesis of these compounds could be optimised by having a better control of reaction conditions, use of different copper sources /different cuprates such as the use of CuCN. In the future, we would try to optimise these step and carry on the synthesis towards hippeastrine. Once a robust route to various analogues of hippeastrine has been developed, further work would concentrate on obtaining hippeastrine in a non-racemic fashion. This work is actually ongoing in our laboratories using an enantiopure chiral cationic iron salt to introduce the desired stereochemistry in the final compound.

3.Experimental Section

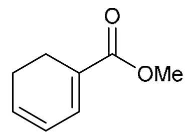
General Methods. Chemicals of reagent grade were used as purchased unless stated otherwise. When mentioned as distilled, THF and Et_2O were freshly distilled from sodium benzophenone ketyl. DCM and acetonitrile were distilled from calcium hydride. Toluene was distilled from sodium. All non-aqueous reactions were carried out under oxygen-free nitrogen or argon using flame-dried glassware. Organolithium reagents were titrated according to the procedure reported by Burchat[84], using *N*-benzylbenzamide. Flash column chromatography was carried out using Davisil LC60A 40-63 micron silica (amorphous silicon dioxide). Thin layer chromatography was carried out using commercially available Macherey-Nagel pre-coated TLC-sheets (ALUGRAM® SIL G/UV_{254} silica plates). Microwave experiments were run with a Biotage Initiator Robot Sixty. Proton and carbon NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer with a 5 mm broad band observe BBFO^{plus} smart probe™ fitted with an actively shielded z-gradient coil (500 MHz). NMR signals were measured using the residual non-deuteriated NMR solvent signal as a reference (for ^1H NMR, $CHCl_3$ at 7.27 ppm and DMSO at 2.50 ppm). For ^{13}C NMR, $CDCl_3$ at 77.0 ppm and DMSO-d_6 at 39.51 ppm were used. Melting points were measured on a Buchi melting point B-545 apparatus. Infra-red spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer. Chemical ionisation and high resolution mass spectra were measured at the EPSRC Mass Spectrometry Centre at the University of Wales, Swansea.

3.1. Preparation of (3-methoxycarbonylallyl)triphenylphosphonium bromide [73] (94)



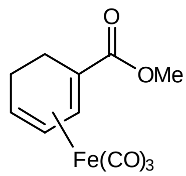
Methyl 4-bromocrotonate **93** (17.1 mL, 0.12 mol) was added dropwise to a solution of triphenylphosphine (32.0 g, 0.12 mol) fully dissolved in toluene (200 mL). The reaction mixture was stirred at room temperature for 2 days, forming a white precipitate. This white precipitate was collected by filtration, washed with toluene and diethyl ether and dried under vacuum to afford the product as white crystals **94** (52.4 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.89 (m, 15H), 6.72 (td, *J*= 13.9, 7.6 Hz 1H), 6.47 (dd, *J* = 15.5, 4.9 Hz, 1H), 5.25 (ddd, *J*= 16.4, 7.6, 1.2 Hz, 2H), 3.65 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4 (d, $J_{C\text{-}P}$ = 2.8 Hz), 135.3 (d, $J_{C\text{-}P}$ = 3.0 Hz), 134.0, 133.9, 132.6, 130.6, 130.5, 130.4, 130.3, 130.2, 129.0, 117.9, 117.2, 51.8, 27.9 ($J_{C\text{-}P}$ = 51 Hz). IR (NaCl) υ 2857, 1717, 1436, 1111 cm^{-1}

3.2. Preparation of cyclohexa-1,3-dienecarboxylic acid methyl ester [73] (95)



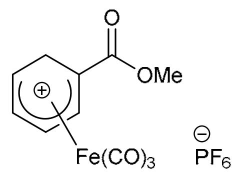
(3-Methoxycarbonylallyl)triphenylphosphonium bromide **94** (52.4 g, 0.12 mol) was dissolved in dichloromethane (928 mL) followed by the addition of saturated hydrogen sodium bicarbonate (742 mL) and acrolein (7.9 mL, 0.12 mol). The reaction mixture was stirred at room temperature for 3 days and the two distinct layers were separated and the organic phase was evaporated under reduced pressure to form a red/ orange oil. The oil was dissolved in a small amount of dichloromethane, evaporated on silica gel and then eluted through a silica column using dichloromethane as the solvent system to give a colourless oil **95** (8.5 g, 51.3 %), Rf: 0.67, ^{1}H NMR (500MHz, $CDCl_3$) δ 6.97 – 6.99 (dd, *J*= 5.4, 0.9 Hz, 1H), 6.10 – 6.15 (m, 1H), 6.01 – 6.07 (ddt, *J*= 9.3, 5.4, 1.9 Hz, 1H), 3.74 (s, 3H), 2.41 – 2.47 (tt, *J*=10.4, 2.8 Hz, 2H), 2.22 – 2.28 (m, 2H), ^{13}C NMR (126MHz, $CDCl_3$) δ 167.9, 133.5, 133.2, 127.1, 123.9, 51.5, 22.8, 20.7, IR (NaCl) υ 2952, 1715, 1683, 1436, 1268 cm^{-1}

3.3. Preparation of tricarbonyl(cyclohexa-1,3-dienecarboxylic acid methyl ester)iron(0)[73] (96)



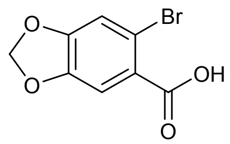
Diiron nonacarbonyl (51.5 g, 0.14 mol) was introduced into a round bottomed flask and nitrogen was flushed through, then dry THF (76.4 mL) was added until a slurry is formed. Cyclohexa-1,3-dienecarboxylic acid methyl ester **95** (8.5 g, 0.06 mol) dissolved in THF (25.2 mL) was added to the slurry. The reaction mixture was flushed one more time with nitrogen and stirred at 68 °C for 5 hours. The mixture was passed through a sinter funnel filled with Kieselguhr and washed with diethyl ether. Silica gel was added to the filtrate which was then evaporated under reduced pressure and purified by silica gel column chromatography (petroleum ether/EtOAc, 80:20) to afford **96** as a yellow oil (5.28 g, 32 %). Rf= 0.75, ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (s, 1H), 5.36 (s, 1H), 3.70 (s, 3H), 3.37 (s, 1H), 2.17 (t, *J*= 12.5 Hz, 1H), 1.92 (t, *J*= 13.0 Hz, 1H), 1.69 (d, *J*= 12.9 Hz, 1H), 1.44 (d, *J*= 10.4 Hz, 1H). ^{13}C (126 MHz, $CDCl_3$) δ 210.2, 172.6, 133.5, 123.9, 88.4, 64.6, 51.6, 25.1, 22.8, IR (NaCl) υ 2951, 2052, 1977, 1712 cm^{-1}

3.4. Preparation tricarbonyl(η[5] -carboxylic acid methyl ester)iron(1+) hexafluorophosphate (1−)[77] (97)



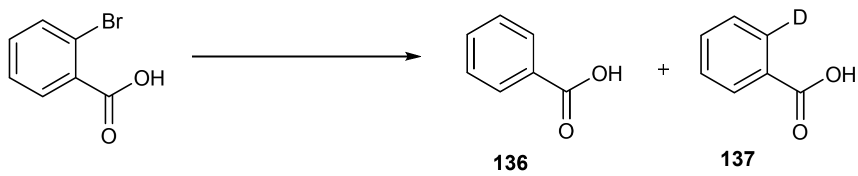
Triphenylcarbenium hexafluorophosphate (12.7 g, 0.03 mol) was dissolved in a minimum volume of dichloromethane (40 mL) under nitrogen atmosphere. The tricarbonyl(cyclohexa-1,3-dienecarboxylic acid methyl ester)iron(0) **96** (6.5 g, 0.02 mol) which had previously been prepared was also dissolved in a minimum amount of dichloromethane (15 mL) under nitrogen atmosphere and was slowly poured into the triphenylcarbenium hexafluorosphosphate solution. The resulting dark mixture was stirred overnight at room temperature and was slowly added to diethyl ether (165 mL). A bright yellow precipitate formed and was collected by filtration and washed with diethyl ether and dried under vacuum to afford yellow solid (7.1 g, 72%). ^{1}H NMR (500 MHz, CD_3CN) δ 7.30 (s, 1H), 6.56 (d, *J* = 5.1 Hz, 1H), 5.89 (s, 1H), 4.70 (t, *J*= 6.3 Hz, 1H), 3.82 (s, 3H), 3.28 (dd, *J*= 15.5, 6.3 Hz, 1H), 1.91 (d, *J*=15.5 Hz, 1H). ^{13}C (126 MHz, CD_3CN) δ 209.2, 117.9, 104.7, 102. 5, 90.7, 71.6, 53.9, 23.9, IR (NaCl) υ 2123, 2064, 1721 cm^{-1}.

3.5. Preparation of 6- bromopiperonylic acid[79] (98)



t-BuOH (60 mL) and water (150 mL) were added to 6-bromopiperonal (6.0 g, 0.03 mol) and the mixture was heated to reflux at 83 ^{o}C. When the reaction mixture achieved this temperature, a solution of potassium permanganate (4.0 g, 0.03 mol) in water (75 mL) was poured in over a period of 45 minutes. The reaction mixture turned brown and was refluxed overnight at 83 ^{o}C and then a solution of 10% potassium hydroxide (30 mL) was added to the warm brown suspension which raised the pH to 10-11. The suspension was filtered and the filtrate was extracted with diethyl ether (4 × 100 mL). The colourless aqueous layer was acidified with concentrated HCl (12 mL) to precipitate a white chalky solid **98** which was collected by filtration and dried under vacuum over phosphorus pentoxide (1.76 g, 27 **%**), m.p.: 206-208 °C (lit, mp: 203-204 °C)[85], ^{1}H NMR (500 MHz, DMSO) δ 13.14 (s, 1H), 7.31 (s, 1H), 7.29 (s, 1H), 6.15 (s, 2H). ^{13}C (126 MHz, DMSO-*d6*) δ 166.9, 150.8, 147.4, 126.4, 114.1, 113.37, 110.7, 103.2, IR (NaCl) υ 3410, 1654, 1648 cm^{-1}

3.6. General procedure for the preparation of lithiation and deuteration of 2-bromobenzoic acid



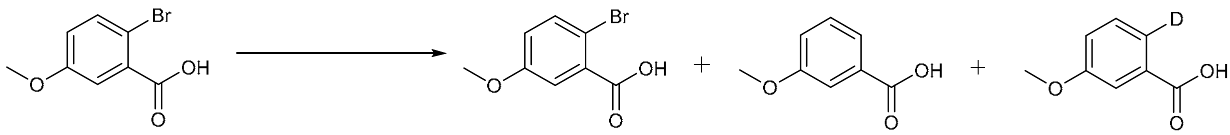
Method 1: *n*-Butyllithium (1.6 mol dm^{-3} solution in hexanes; 0.31 mL, 0.99 mmol) was added dropwise to a solution of 2-bromobenzoic acid (0.1 g, 0.49 mmol) in THF (9 mL) at −78 °C and the reaction mixture appeared pale yellow. The reaction was stirred for 2 hours and was quenched with deuterium oxide (0.1 mL) and was quenched with 1M HCl (17 mL) and the aqueous phase was extracted with dichloromethane (3 × 50 mL).The product was obtained as a white solid (0.03 g, 57%) which was dried over calcium chloride. The crude was characterised .

137 ^{1}HNMR (500 MHz, DMSO) δ 12.93 (s, 1H), 7.96 – 7.93 (m, 1.47H), 7.64 – 7.60 (m, 1H), 7.52 – 7.48 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 169.6, 141.2, 129.5, 128.9, 126.99, 127.9, 127.5, 127.3

Benzoic acid

136 ^{1}H NMR (500 MHz, DMSO),δ 12.93 (s, 1H), 7.96 – 7.93 (m, 2H), 7.64 – 7.50 (m, 1H), 7.52 – 7.46 (m, 2H). ^{13}C (126 MHz, DMSO) δ 169.6, 141.2, 129.5, 128.9, 127.9, 127.5, 127.3.

3.7. General procedure for the preparation of lithiation and deuteration of 2-bromo-5-methoxy benzoic acid



140 140 138 139

Method 2: LiHMDS (2.00 mL, 2.00 mmol) was added to a solution of 2-bromo-5-methoxy benzoic acid (0.5 g, 2.00 mmol) in THF (30 mL) over a 10 min period. The reaction was warmed at 0 °C then cooled back at −78 °C, then n- butyllithium (1.6 mol dm^{-3} solution in hexanes; 2.5 mL, 4.00 mmol) was added dropwise. The reaction was stirred for 2 hours then deuterium oxide was added (0.10 mL). The reaction was quenched with 1M HCl (17 mL) and the aqueous phase was extracted with dichloromethane (3 × 50 mL) and dried under vacuum to afford the crude as a white solid (0.068 g).

2-Bromo-5-methoxbenzoic acid

140 ^{1}H NMR (500 MHz, DMSO) δ 13.01 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 3.2 Hz, 1H), 7.02 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 167.6, 159.7, 132.6, 130.1, 122.0, 119.4, 114.3, 55.7.

5-Methoxybenzoic acid

138 ^{1}H NMR (500 MHz, DMSO) δ 13.01 (s, 1H), 7.55-7.52 (m, 1H), 7.44 (d, *J* = 2.7 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 1H), 7.19 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 167.6, 159.7, 130.1, 122.0, 119.4, 114.3, 55.7. (Yield, 22 %)

Deuterated 2-bromo-5-methoxy benzoic acid

139 ^{1}H NMR (500 MHz, DMSO) δ 13.01 (s, 1H), 7.44 (d, *J* = 2.7 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 1H), 7.19 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 167.6, 159.7, 132.6, 130.1, 122.0, 119.4, 116.07 114.3, 55.7. (Yield, 63%)

Method 3: NaH (0.05 g, 2.00 mmol **Entry: 1**; 0.10 g, 4.00 mmol **Entry 2**) was added to a solution of 2-bromo-5-methoxy benzoic (0.46 g, 2.00 mmol) in THF (30 mL) at −78 °C. A white precipitate formed. The reaction mixture was allowed to warm up at room temperature and a white precipitate disappeared. Once the reaction mixture reached room temperature, it was cooled to −78 °C and then *n*-butyllithium (1.6 mol dm^{-3} solutions in hexanes; 1.25 mL, 2 mmol) was added dropwise. The reaction was stirred for 1 hour and deuterium oxide was added (0.10 mL). The reaction was quenched with 1M HCl (17 mL) and the aqueous phase was extracted with dichloromethane (3 × 50 mL).

Entry 1

White solid (0.287 g).

2-Bromo-5-methoxy-benzoic acid

140 ^{1}H NMR (500 MHz, DMSO) δ 13.13 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 3.2 Hz, 1H), 7.02 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.80 (s, 3H).

5-Methoxy-benzoic acid

138 ^{1}H NMR (500 MHz, DMSO) δ 13.13 (s, 1H), 7.54– 7.51 (m,1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.41 (t, *J* = 8.3 Hz, 1H), 7.18 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.80 (s, 3H).

Deuterated 2-bromo-5-methoxy benzoic acid

139 ^{1}H NMR (500 MHz, DMSO) δ 13.13 (s, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.41 (t, *J* = 8.3 Hz, 1H), 7.18 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.80 (s, 3H).

Entry 2:

White solid (0.281 g).

2-Bromo-5-methoxy benzoic acid

140 ^{1}H NMR (500 MHz, DMSO) δ 13.04 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 3.2 Hz, 1H), 7.02 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.80 (s, 3H).

5-Methoxy-benzoic acid

138 ^{1}H NMR (500 MHz, DMSO) δ 13.04 (s, 1H), 7.54– 7.51 (m,1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.41 (t, *J* = 8.3 Hz, 1H), 7.18 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.80 (s, 3H).

Deuterated 2-bromo-5-methoxy benzoic acid

139 ^{1}H NMR (500 MHz, DMSO) δ 13.04 (s, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.41 (t, *J* = 8.3 Hz, 1H), 7.18 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.80 (s, 3H).

Method 4: Methyllithium (1.6 mol dm^{-3} solution in diethyl ether; 2.02 mL, 3.24 mmol) was added to a solution of 2-bromo-5-methoxy benzoic (0.5 g, 2.16 mmol) in THF (30 mL) at −78 °C. The reaction mixture turned pale yellow. The reaction mixture was allowed to warm up at −40 °C for a period of (15-30 min). Once the reaction mixture reached −40 °C, it was cooled back to −78 °C and then *n*-butyllithium (1.6 mol dm^{-3} solution in hexanes; 1.35 mL, 2.16 mmol) was added dropwise and the solution turned orange / dark yellow. The reaction was stirred for 1 hour and appeared yellow and deuterium oxide was added (0.10 mL). The reaction was quenched with 1M HCl (17 mL) and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The product was obtained as a white solid (0.283 g).

2-Bromo-5-methoxy benzoic acid

140 ^{1}H NMR (500 MHz, DMSO) δ 13.29 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 3.2 Hz, 1H), 7.02 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.80 (s, 3H).

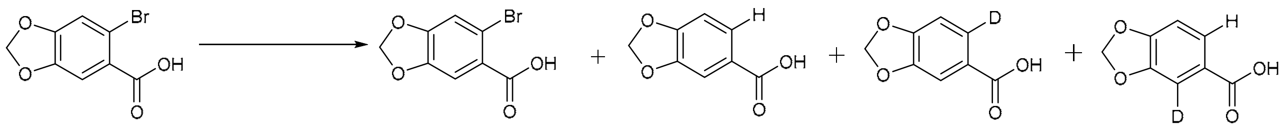
5-Methoxy-benzoic acid

138 ^{1}H NMR (500 MHz, DMSO) δ 13.29 (s, 1H), 7.54 – 7.52 (m ,1H), 7.44 (d, *J* = 2.5 Hz, 1H), 7.41 (t, *J* = 8.3 Hz, 1H), 7.18 (dd, *J* = 8.0, 2.3 Hz, 1H), 3.80 (s, 3H).

Deuterated 2-bromo-5-methoxy benzoic acid

139 ^{1}H NMR (500 MHz, DMSO) δ 13.29 (s, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.41 (t, *J* = 8.3 Hz, 1H), 7.18 (dd, *J* = 8.0, 2.3 Hz, 1H), 3.80 (s, 3H).

3.8. General procedure for the preparation of lithiation and deuteriation of 6-bromopiperonylic acid



98   98   148   149   150

Method 5: *n*- butyllithium (1.6 mol dm^{-3} solution in hexanes; 2 equivalents) was added dropwise to a solution of 6-bromopiperonylic acid (1 equivalent) in THF (20 mL) at −100 °C. The reaction was stirred for various times and deuterium oxide was added (0.10 mL). The reaction was quenched with 1M HCl (17 mL) and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The crude appeared as a white solid (0.10 g)

149 ^{1}H NMR (500 MHz, DMSO) δ 12.96 (s, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.15 (s, 2H).

150 ^{1}H NMR (500 MHz, DMSO) δ 12.96 (s, 1H), 7.55 (d, *J* = 8.1 Hz, 1 H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.15 (s, 2H).

148 ^{1}H NMR (500 MHz, DMSO) δ 12.96 (s, 1H), 7.55 (d, *J* = 8.1 Hz, 1 H), 7.35 (s, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.15 (s, 2H).

Method 6: LiHMDS (1.2 equivalents **Entry 3**, **Entry 4, Entry 5**, 1.1 equivalents **Entry 6**) was added over a 10 min period at various temperatures, then *n*- butyllithium (1.6 mol dm^{-3} solution in hexanes; 2 equivalent) was added dropwise to a solution of 6- bromopiperonylic acid (1 equivalent) in THF (30 mL). The reaction was stirred for various times deuterium oxide was added (0.10 mL). The reaction was quenched with 1M HCl (17 mL) and the aqueous phase was extracted with dichloromethane (3 × 50 mL).

Entry	temperature	time
Entry 3 Brown/yellow solid 0.122 g	LiHMDS at −78 °C, warm at 0 °C, deuteriation and lithiation at −78 °C	1 hr 30 min 2 hrs
Entry 4 Brown/yellow solid 0.174 g	LiHMDS at −78 °C, warm at 0 °C, deuteriation and lithiation at −78 °C	1hr 30 min 2hrs
Entry 5 Brown/ yellow solid 0.014 g	LiHMDS at −78 °C, warm at 0 °C, deuteriation and lithiation at −78 °C	2 hr 30 min 2 hr
Entry 6 Brown/yellow solid 0.059 g	LiHMDS at −78 °C, warm at 0 °C, deuteriation and lithiation at −78 °C	1 hr 30 min 1 hr

Deuterated product- Entry 3

149 ^{1}H NMR (500 MHz, DMSO) δ 12.75 (s, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.15 (s, 2H).

150 ^{1}H NMR (500 MHz, DMSO) δ 12.75 (s, 1H), 7.55 (d, *J* = 8.15 Hz, 1 H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.15 (s, 2H).

148 ^{1}H NMR (500 MHz, DMSO) δ 12.75 (s, 1H), 7.55 (d, *J* = 8.15 Hz, 1 H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.15 (s, 2H).

Deuterated product- Entry 4

149 ^{1}H NMR (500 MHz, DMSO) δ 12.74 (s, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

150 ^{1}H NMR (500 MHz, DMSO) δ 12.74 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

148 ^{1}H NMR (500 MHz, DMSO) δ 12.74 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

Deuterated product- Entry 5

149 ^{1}H NMR (500 MHz, DMSO) δ 12.74 (s, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

150 ^{1}H NMR (500 MHz, DMSO) δ 12.74 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

148 ^{1}H NMR (500 MHz, DMSO) δ 12.74 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

deuterated product- Entry 6

149 ^{1}H NMR (500 MHz, DMSO) δ 12.84 (s, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

150 ^{1}H NMR (500 MHz, DMSO) δ 12.84 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

148 ^{1}H NMR (500 MHz, DMSO) δ 12.84 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

Method 7: NaH (0.05 g, 2 mmol **Entries 7 and 8;** 0.10 g, 4 mmol **Entry 9**) was added to a solution of 6-bromopiperonylic acid (0.25 g, 1 mmol **Entries 7 and 8 ;** 0.49 g, 2 mmol **Entry 9**) in THF (30 mL) at different temperature. A white precipitate formed. The reaction mixture was allowed was allowed to cool down at −78 °C and then n-butyllithium (1.6 mol dm^{-3} solution in hexanes; 1.25 mL, 2 mmol) was added dropwise. The reaction was stirred (various times and temperatures) and deuterium oxide was added. The reaction was quenched with 1M HCl (17 mL) and the aqueous phase was extracted with dichloromethane (3 × 50 mL).

Entry	Temperature	Time
Entry 7 White/ yellow solid 0.5 g	NaH at −78 °C, warm at r.t, deuteriation and lithiation at −78 °C	1 min 30 min 2hrs
Entry 8 Brown solid 0.129 g	NaH at −78 °C, warm at r.t, deuteriation and lithiation at −78 °C	1 min 30 min 2hrs
Entry 9 Yellow solid 0.031 g	NaH at −78 °C, warm at r.t, lithiation at −78 °C, warm the reaction between −40 to −20 °C, deuteriation at −78 °C	1 min 30 min 10 min 1hr 30 min Few seconds

Deuterated product- Entry 7

146 ^{1}H NMR (500 MHz, DMSO) δ 13.02 (s, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

147 ^{1}H NMR (500 MHz, DMSO) δ 13.02 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1 H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

145 ^{1}H NMR (500 MHz, DMSO) δ 13.02 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1 H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

deuterated product- Entry 6

149 ^{1}H NMR (500 MHz, DMSO) δ 13.03 (s, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

150 ^{1}H NMR (500 MHz, DMSO) δ 13.03 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

148 ^{1}H NMR (500 MHz, DMSO) δ 13.03 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

Deuterated product- Entry 7

149 ^{1}H NMR (500 MHz, DMSO) δ 11.61 (s, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

150 ^{1}H NMR (500 MHz, DMSO) δ 11.61 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

148 ^{1}H NMR (500 MHz, DMSO) δ 11.61 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 2H).

Method 8: Methyllithium (1.6 mol dm^{-3} solutions in diethyl ether; 1.53 mL, 2.45 mmol) was added to a solution of 6-bromopiperonylic acid (0.4 g, 1.63 mmol) in THF (30 mL) at - 78˚C. The reaction mixture was stirred (various temperatures and times). Once the reaction mixture reached the desired temperature, it was cooled back to -78 ˚C and then n-butyllithium (1.6 mol dm^{-3} solution in hexanes; 1.35 mL, 2.16 mmol) was added dropwise. The reaction was stirred for various times, followed by a deuterium oxide addition (0.10 mL). The reaction was quenched with 1M HCl (17 mL) and the aqueous phase was extracted with dichloromethane (3 × 50 mL).

Entry	Temperature	Time
Entry 10 White solid 0.286 g	MeLi at −78 °C, deuteriation and lithiation at −78 °C	10 min 1 hr
Entry 11 White solid 0.214 g	MeLi at -78 °C, deuteriation and lithiation at −78 °C	4 hrs 1 hr

Deuterated product- Entry 10

149 ^{1}H NMR (500 MHz, DMSO) δ 12.71 (s, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.11 (s, 2H).

150 ^{1}H NMR (500 MHz, DMSO) δ 12.71 (s, 1H), 7.55 (d, *J* = 8.15 Hz, 1 H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.11 (s, 2H).

148 ^{1}H NMR (500 MHz, DMSO) δ 12.71 (s, 1H), 7.55 (d, *J* = 8.15 Hz, 1 H), 7.35 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.11 (s, 2H).

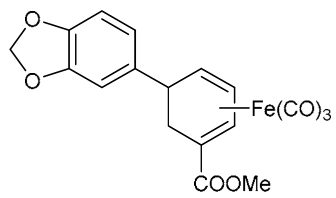
Deuterated product- Entry 11

149 ^{1}H NMR (500 MHz, DMSO) δ 12.64 (s, 1H), 7.35 (s, 1H), 7.00 (d, *J* = 8.15 Hz, 1H), 6.11 (s, 2H).

150 ^{1}H NMR (500 MHz, DMSO) δ 12.64 (s, 1H), 7.54 (d, *J* = 8.15 Hz, 1 H), 7.00 (d, *J* = 8.15 Hz, 1H), 6.11 (s, 2H).

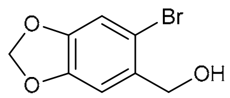
148 ^{1}H NMR (500 MHz, DMSO) δ 12.64 (s, 1H), 7.55 (d, *J* = 8.15 Hz, 1 H), 7.35 (s, 1H), 7.00 (d, *J* = 8.15 Hz, 1H), 6.11 (s, 2H).

3.9. Preparation of tricarbonyl [ŋ^4-1-methyl ester-5-(3',4'-methylenedioxy)phenylcyclohexa- 1,3-diene]iron(0)[81] (134)



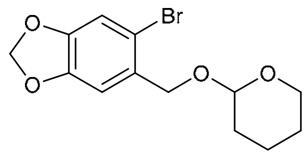
n- Butyllithium (2.5 mol dm^{-3} solution in hexanes; 1.19 mL, 2.98 mmol) was added dropwise to a solution of 4-bromo-1,2-(methylenedioxy)benzene (**132)** (0.30 mL, 2.48 mmol) in THF (40 mL) at −78 °C and the reaction mixture appeared pale yellow. The mixture was stirred for 2 hours at −78 °C and then CuBr (0.18 g, 1.24 mmol) was added and the reaction appeared brown. After the mixture had been stirred for a further 10 minutes, its temperature was allowed to rise to −40 °C at which point the substrate tricarbonyl(ŋ^5 -carboxylic acid methyl ester) iron (1+) hexafluorophosphate (1−) (0.68 g, 1.07 mmol) was added and the mixture became dark brown. The mixture was warmed to 0 °C and turned black. The reaction was quenched with 2M HCl (17 mL). The aqueous phase was extracted with diethyl ether (3 × 50 mL) to give a dark yellow residue after drying and solvent removal. Column chromatography on silica gel with diethyl ether / hexane (1:10) afforded the title compound. (0.19 g**,** 19 **%**). ^{1}HNMR (500 MHz, $CDCl_3$) δ 6.67 (d, *J* = 7.8 Hz, 1H, 3'- and 5'-H), 6.59 – 6.54 (m, 2H, 6'-H), 6.24 (d, *J* = 4.0 Hz, 1H, 2-H), 5.90 (s, 2H, OCH_2O), 5.46 (dd, *J* = 6.3, 4.5 Hz, 1H, 3-H), 3.71 (s, 3H, OMe), 3.42 (dt, *J* = 11.4, 3.7 Hz, 1H, 5-H), 3.28 (ddd, *J* = 6.2, 3.3, 1.1 Hz, 1H, 4-H), 2.77 (dd, *J* = 11.4, 11.5 Hz, 1H, 6β-H), 1.44 (dd, *J* = 15.5, 4.0 Hz, 1H, 6α-H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.85 (s, $Fe(CO)_3$), 172.3 (C=O), 147.8 (s, 4'- or 3'-C), 146.1 (s, 3'- or 4'-C), 140.00 (s, 2-C), 120.0 (s, 6'-C) 108.1 (s, 5'- or 2'-C), 106.9 (s, 2'- or 5'-C), 100.9 (s, OCH_2O), 89.0 (s, 3-C), 84.3 (s, s, 4- or 1-C), 62.7 (s, OMe), 51.7 (s, 1- or 4-C), 45.5 (s, 5-C), 32.4 (s, 6-C). IR (NaCl) υ 2053, 1979, 1233 cm^{-1}, HRMS $[M+H]^+$ Calculated for $C_{18}H_{15}FeO_7$: 398.01; Found: 399.0162.

3.10. Preparation of 2- bromo- 4,5- methylenedioxybenzyl alcohol (151)[83]



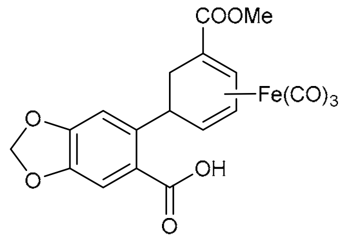
3,4-methylenedioxybenzyl alcohol (5 g, 33 mmol) was dissolved in dichloromethane (51 mL) and the solution was cooled in an ice bath. *N*-Bromosuccinimide (5.85, 33 mmol) was added over a period of 20 minutes and the reaction mixture was stirred for 2 hours at 5 °C. 10% aqueous sodium sulphite (1.29 M, 25.5 mL) was added and the two layers were stirred for 5 min. The organic phase was separated from the aqueous layer. The aqueous layer was washed with dichloromethane (2×51 mL) and the organic phases were combined and dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give the white solid 2-bromo-4,5-methylenedioxybenzyl alcohol **151** (7.2 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) 1H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.97 (s, 1H), 5.97 (s, 2H), 4.63 (s, 2H), 2.75 (s, 1H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.80, 147.55, 133.12, 113.02, 112.70, 109.15, 101.79, 64.93. IR (NaCl) υ 3417, 2901, 1480 cm^{-1} .

3.11. Preparation of 2-bromo-4,5-methylenedioxybenzyl 1-tetrahydropyranyl ether (152) [83, 86]



2- Bromo- 4,5- methylenedioxybenzyl alcohol **151** (7.24 mL, 31 mmol) was dissolved in dichloromethane (49 mL), then pyridinium *p*-toluenesulfonate (8.5 mg, 0.034 mmol) and 3,4-dihydro-2H-pyran (2.87 mL, 31 mmol) were added. The reaction was stirred overnight at room temperature and water (24 mL) was added. The two layers were separated and the aqueous phase was extracted with dichloromethane (49 mL). The organic phases were combined and the solvent was evaporated at reduced pressure. The compound was dissolved in a small amount of dichloromethane, evaporated under reduced pressure on silica gel and then eluted through a silica column using hexane / EtOAc (95:5) as the solvent system to yield a colourless oil **152** (8.7 g, 89 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.99 (s, 1H), 5.96 (s, 2H), 4.74 (s, 1H), 4.70 (d, *J* = 0.4 Hz, 1H), 4.49 (d, *J* = 12.8 Hz, 1H), 3.95 – 3.88 (m, 1H), 3.59 – 3.54 (m, 1H), 1.91 – 1.48 (m, 6H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.57, 147.39, 131.08, 113.19, 112.60, 109.27, 101.68, 98.30, 68.49, 62.22, 30.53, 25.45, 19.36, IR (NaCl) υ 2942, 1479, 1245, 1035 cm^{-1}.

3.12. Preparation of tricarbonyl[η^4-1-methyl Ester-5-(3',4'-methylenedioxy-6'-carboxyphenyl) cyclohexa- 1,3-diene]iron(0)[81] (99)



n- butyllithium (2.5 mol dm^{-3} solution in hexanes; 0.8 mL, 2 mmol) was added dropwise to 6-bromopiperonylic acid (0.5 g, 1 mmol) in THF (40 mL) at −78 °C and the reaction mixture appeared yellow. The mixture was stirred for 2 hours at −78 °C and then CuBr (0.07 g, 0.5 mmol) was added and the reaction remained yellow. After the mixture had been stirred for a further 10 minutes, its temperature was allowed to rise to −40 °C at which point the substrate tricarbonyl (η^5 -carboxylic acid methyl ester) iron (1+) hexafluorophosphate (1−) (0.12 g, 0.47 mmol) was added and the mixture became brown. The mixture was warmed to 0 °C and was still brown. The reaction was quenched with 2M HCl (17 mL). The two phases were separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The organic layers were combined to give a dark yellow residue after drying over magnesium sulfate, filtration and solvent removal under reduced pressure. Column chromatography on silica gel eluted with diethyl ether / hexane (1:10) then 4% methanol in DCM afforded the title compound. (0.12 g, 27 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 1H), 7.41 (s, 1H, ArH), 6.75 (s, 1H, ArH), 6.74 – 6.72 (m, 1H), 6.26 (d, *J* = 4.0 Hz, 1H, 2-H), 6.21 (d, *J* = 4.1 Hz, 1H, 2-H), 6.06 (d, *J* = 1.3 Hz, 1H, O-CH_2-O), 6.02 (d, *J* = 1.4 Hz, 1H, O-CH_2-O), 6.01 (d, *J* = 1.3 Hz, 1H, O-CH_2-O), 5.99 (d, *J* = 1.3 Hz, 1H, O-CH_2-O), 5.52 (dd, *J* = 6.3, 4.4 Hz, 1H, 3-H), 5.40 (dd, *J* = 6.3, 4.5 Hz, 1H, 3-H), 4.68 (dt, *J* = 11.3, 3.8 Hz, 1H, 5-H), 4.62 – 4.58 (m, 1H, 5-H), 3.72 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.38 – 3.35 (m, 2H), 2.88 (dd, *J* = 15.5, 11.5 Hz, 1H, 6β-H), 2.63 (dd, *J* = 15.0, 11.5 Hz, 1H, 6β-H), 1.72 (dd, *J* = 15.1, 4.2 Hz, 1H, 6α-H), 1.36 (dd, *J* = 15.7, 4.1 Hz, 1H, 6α-H).^{13}C NMR (126 MHz, $CDCl_3$) δ 211.3 (s, $Fe(CO)_3$), 172.5 (C=O of the ester), 151.6 (C=O of the carboxylic acid), 145.8, 145.6, 145.1, 129.0, 127.5, 122.5, 121.1, 110.6, 107.1, 106.5, 101.9, 101.5 (O-CH_2-O), 88.9, 88.5, 85.1, 84.5, 67.1, 64.9, 62.9, 62.7, 51.6, 40.3, 37.4, 31.9, 27.8. IR (NaCl) υ 3406, 2953, 2055, 1986, 1704, 1682, 1256 cm^{-1}. HRMS $[M+H]^+$ Calculated for $C_{19}H_{14}FeO_9$: 442.0; Found: 443.0073

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5. Appendix