Part 2

Abstract

Bioisosteres are often used in the pharmaceutical and agrochemical industries as a means to optimise lead compounds, by altering their geometry, pKa, lipophilicity and/or hydrophilicity. A wide range of functional groups have been employed as bioisosteres, however, examples of phosphinates being used are rare. Herein, we report an investigation into whether phosphinates are viable bioisosteres for the sulfone functional group, by the synthesis of phosphinate analogues of known sulfone-containing agrochemical and pharmaceutical compounds. The syntheses of 5 novel *P*-stereogenic phosphinate analogues have been completed in yields ranging from 2 – 26%. The biological activity and/or physical chemistry of these compounds were subsequently tested and the results are reported.

Chapter 1 – Introduction and Project Aims

1.1. Bioisosteres

Bioisosteres have origins as early as 1919 with Langmuirs work on isosterism but it was not until 1951 that the term ‘bioisostere’ was introduced, by Friedman and co-workers.[1–3] The concept was later defined by Thornber as “groups or molecules which have chemical and physical similarities producing broadly similar biological properties”.[4] There are two separate categories for bioisosteres; classical and non-classical, and common examples of each are summarised in Figure 1.[1,2,4,5]

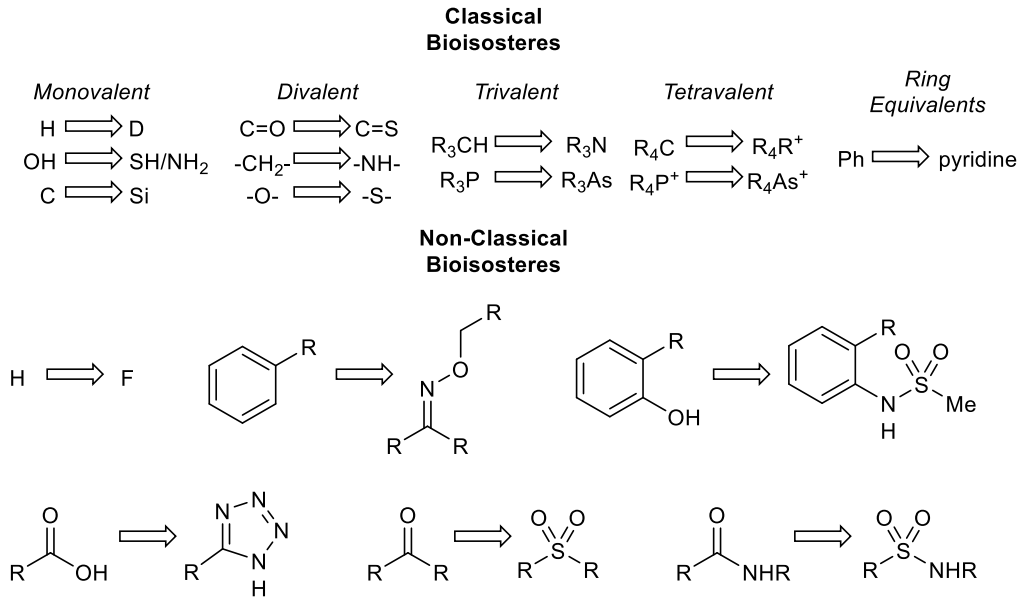


Figure 1: *Selected examples of classical and non-classical bioisosteres.*

Classical bioisosteres are broadly defined as pairs of atoms, molecules or functional groups, with the same number of valence electrons and are subdivided into five categories, Figure 1.[5] Mono-, di-, tri- and tetravalent bioisosteres correspond to the number of bonds which are affected by the interchange of atoms (excluding bonds to hydrogen).[1] Non-classical bioisosteres are less well defined and are simply any bioisosteres that are not encompassed by the definition of a classical bioisostere.

Non-classical bioisosteres are usually more complex with more than one atom being substituted, Figure 1.

The use of bioisosteres in the drug discovery process has become a popular strategy.[2] Bioisosteres would ideally be used as direct mimics for the original functional group; however, in practice this is often not possible. According to Patani and co-workers "the critical component for bioisosterism is that bioisosteres affect the same pharmacological target".[2] In reality, bioisosteres are used to optimise the activity of a compound by altering its structure, pKa, lipophilicity and/or hydrophilicity.[4] It is therefore important to consider size, geometry, polarity, pKa and H-bonding donors and acceptors, when designing a bioisosteres.[1]

1.2. The Sulfone Functional Group

1.2.1. Sulfones in the Pharmaceutical Industry

Sulfur functional groups have often been used as bioisosteres for carbon-based moieties, and have now become integral to drug design.[2] In 2014, it was reported that 362 of 1969 FDA approved drugs contained a sulfur moiety.[6] It was also stated that 29% of sulfur-based pharmaceutical drugs were sulfonamides; with only 2% incorporating a sulfone.[6] Although sulfones represent a low proportion of sulfur-based drugs, they have still made a number of invaluable contributions to the industry, Figure 2.[7–9] Since 1937, approved sulfone drugs have had a significant impact on a range of disease areas, including: cardiovascular, muscular skeletal, anti-infective, nervous system and oncology.[7,8] Sulfones are still considered an essential class of compounds and some selected examples of important sulfone pharmaceutical compounds can be seen in Figure 2.

In 2014, Otezla® **1** was approved for the treatment of psoriatic arthritis and psoriasis, and is a highly successful sulfone-based drug.[10] In 2018, it was amongst

the top 100 pharmaceutical products (by retail sales), with sales of $1.61 billion.[9] Encorafenib **2** represents one of the most recent sulfone-containing drugs on the market, and in 2018 it was approved for the treatment of BRAF mutated melanoma.[11]

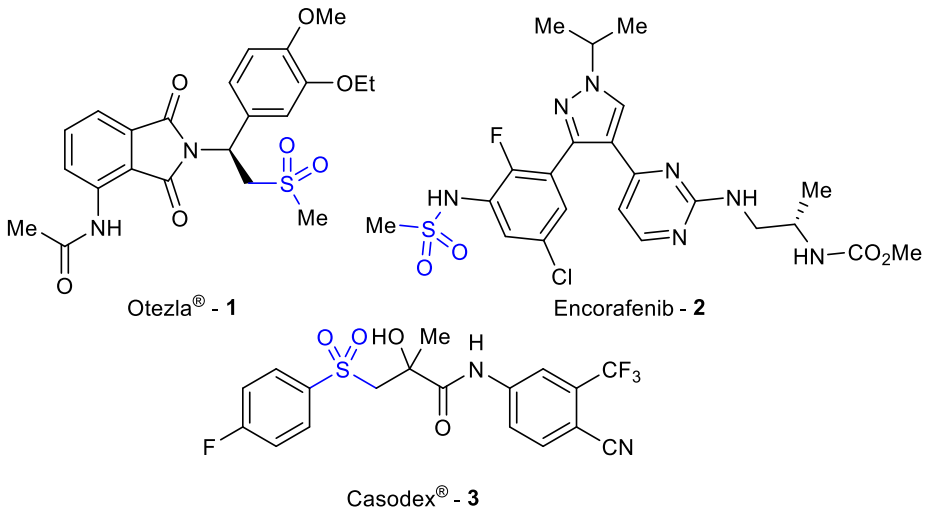


Figure 2: *Structures of some important sulfone containing pharmaceutical compounds.*

The final compound in Figure 2 is Casodex® **3**, which is a non-steroidal anti-androgen developed for the treatment of prostate cancer.[7,12–16] It is a competitive inhibitor of the androgen receptor and therefore inhibits the binding of hormones like testosterone and dihydrotestosterone.[12,14–16] It was observed that in the absence of androgens, cell growth was prevented and cell death occurred, therefore providing inhibition of prostate cancer cells.[12,15] Although Casodex® **3** is a racemate it has been demonstrated that the *R*-enantiomer is responsible for the activity, with the *S*-enantiomer being rapidly metalbolised.[12,15] There is no doubt that Casodex® **3** is an extremely important oncological compound, nevertheless there is now evidence for resistance to the drug, which may lead to additional analogues being required.[17–19]

1.2.2. Sulfones in the Agrochemical Industry

Sulfones are also an essential class of compounds in the agrochemical industry. In 2017, a comprehensive review of sulfur-containing agrochemicals was published by Devendar and Yang.[20] Of the 86 commercial sulfur-based agrochemicals discussed, 16% were sulfones.[20] A high proportion of these sulfones were herbicides categorised as 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) inhibitors.

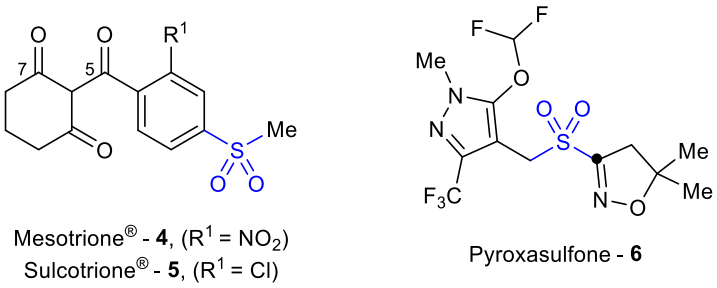


Figure 3: *Selected examples of sulfone-containing agrochemical compounds.*

Mesotrione® **4** and Sulcotrione® **5** are well-known examples of 4-HPPD inhibitors, Figure 3.[20–22] They represent only a small proportion of commercially available methylsulfone containing 4-HPPD inhibitors.[20] 4-Hydroxyphenylpyruvate dioxygenase (4-HPPD) is an iron (II) bound enzyme that is required for the biosynthetic pathway that converts tyrosine to plastoquinone.[22,23] The inhibition of this pathway eventually disrupts chlorophyll production and therefore leads to bleaching of the plant.[21–24] Triketone inhibitors of 4-HPPD are proposed to bind to the iron centre of the enzyme *via* the 5 and 7 carbonyl moieties, with an additional key π-stacking interaction with a phenylalanine residue.[25] Alternative 4-HPPD inhibitors that do not contain the 1,3-diketone structure must bind in a different manner.[25] For example the sulfone-based herbicide **7**, reported by BASF,[26] is also suspected to be a 4-HPPD inhibitor, Figure 4. At physiological pH **7** it has been proposed that it binds to 4-HPPD *via* the co-ordination with its pyridine nitrogen and enolate oxyanion, Figure 4.

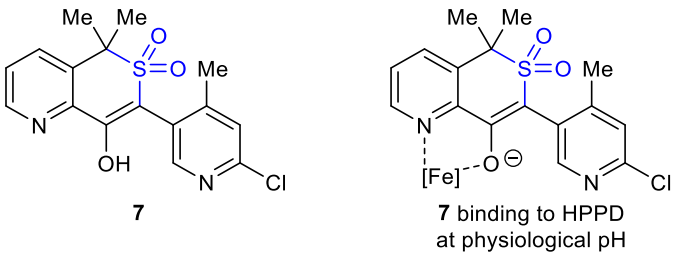
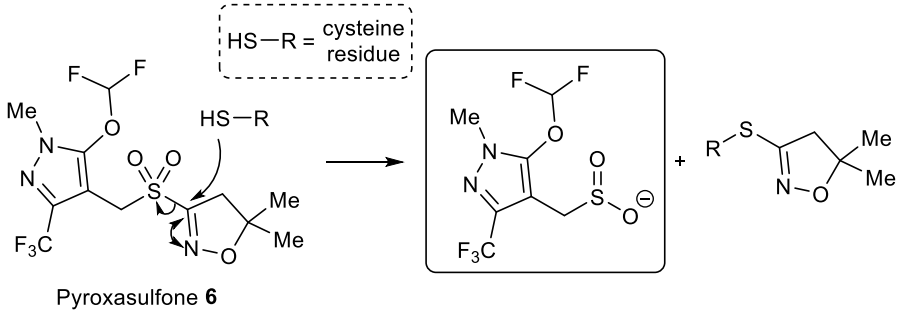


Figure 4: *The structure and proposed binding of the BASF reported herbicide* ***7****.*

Not all sulfone-based agrochemicals are 4-HPPD inhibitors. One example, pyroxasulfone **6**, is a herbicide that was approved for use in Australia, USA, Canada, Japan, South Africa and Saudi Arabia, Figure 3.[27,28] It is a pre-emergence herbicide that is used in production of a range of crops including: wheat, soy bean, cotton, turf and corn.[27,28] It is an inhibitor of the very-long-chain fatty acid elongase (VLCFAE), which disrupts the production of very-long-chain fatty acids (VLCFAs) and prevents the target seed from growing.[27–29] Pyroxasulfone **6** is thought to be a covalent inhibitor that binds to the target enzyme by the nucleophilic attack of a cysteine residue with the electrophilic isoxazoline carbon, Scheme 1.[29,30]



Scheme 1: *The mode of action of Pyroxasulfone* ***6****.*

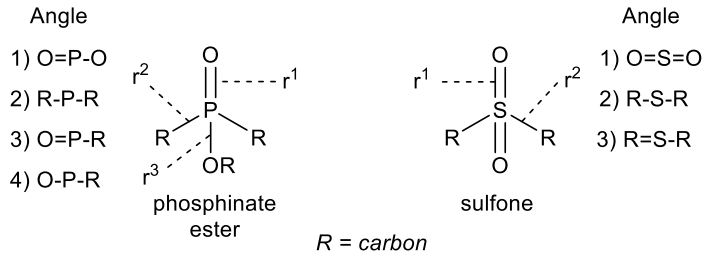
In this section it has been demonstrated that sulfones play an important role in both the agrochemical and pharmaceutical industries. The examples that have been discussed have highlighted the diversity of sulfone compounds in a range of biological applications. Herein, the concept that the phosphinate functional group could act as a bioisosteric replacement for the sulfone moiety will be discussed.

1.3. Phosphinates as Bioisosteric Replacements for the Sulfone Functional Group

1.3.1. Structural Comparisons

A search of the Cambridge Structural Database (CSD) provided an insight into the structural similarities between sulfones and phosphinate esters, Table 1. The dataset allowed for the direct comparison of bond lengths and bond angles, of 4736 sulfones and 298 phosphinates.

Table 1: *A comparison of bond lengths and bond angles between phosphinates and sulfones.*



	No.	r^1 / Å	r^2 / Å	r^3 / Å	Angle1	Angle2	Angle3	Angle4
Sulfone	4736	1.44	1.78	N/A	118.3	103.6	108.4	N/A
Phosphinate	298	1.47	1.80	1.59	114.6	107.2	113.5	103.5

The data indicated that the mean bond lengths of phosphinates and sulfones were very similar. The average bond length of a *S-O* double bond was 1.44 Å, compared to 1.47 Å for a *P-O* double bond. A similar observation can be drawn from the *S-C* and *P-C* bonds, where the *S-C* bond is on average 0.02 Å longer. Unsurprisingly, the *P-O* single bond was found to be longer than both the *P-O* and the *S-O* double bonds, with a mean average bond length 1.59 Å.

There were some differences in the geometry of the two functional groups which could be seen when examining their bond angles, Table 1. The first difference was that the *O-S-O* bond angle was on average 3.7 ° larger than the *O-P-O* bond angle.

Consequentially, this meant that the *R-S-R* bond angle was 3.6 ° smaller than the *R-P-R* bond angle. The second difference to note was that all the *R-S=O* bond angles are on average 108.4 °. However, because a phosphinate contains one *P-O* single bond and one *P-O* double bond, the angles between these bonds and the R groups were different. *The R-P-O* bond angle was 103.5 ° and the *R-P=O* bond angle was 113.5 °. Although there was a difference in bond angles overall the geometries of the two functional groups were comparable.

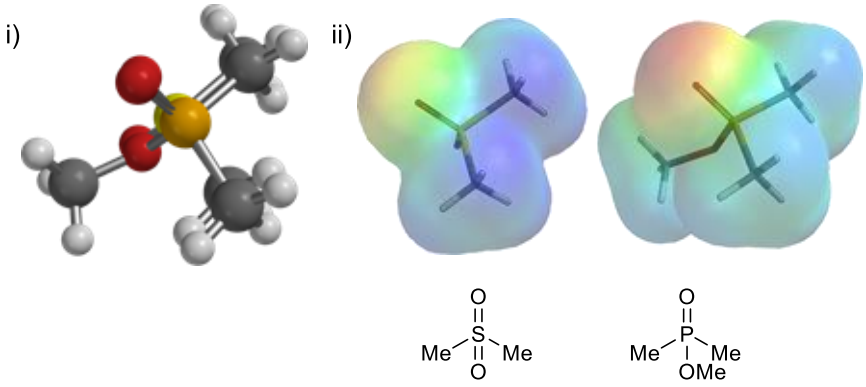


Figure 5: *i) An overlay of the B3LYP/6-31G* minimized structures of the representative sulfone and phosphinate moieties b) Minimised structures with electron density surfaces*

Distinct structural similarities could be observed when a representative sulfone and phosphinate were overlaid with each other, Figure 5i. Furthermore, when the electrostatic potential was mapped onto an electron density surface the position of the hydrogen bond acceptor was shown to be comparable, Figure 5ii.

Phosphinates have some benefits over sulfone functional groups. Firstly, they can possess a *P*-stereogenic phosphorus centre which can be potentially advantageous for when optimising the structure for selective binding. Secondly, phosphinates have an additional handle for further functionalisation if required, however, for this particular investigation only methylphosphinate esters will be synthesised because it was thought that a smaller ester group would mimic a sulfone to a greater extent.

1.3.2. Phosphinates in Industry

Examples of pharmaceutical and agrochemical compounds containing the phosphinate moiety are rare. However, there are some important examples in the literature, Figure 6 and Scheme 2.[31,32] One of which is Fosinopril **8**, a complex phosphinate ester that was approved for the treatment of hypertension and heart failure. The phosphinate is the prodrug which upon hydrolysis releases the active phosphinic acid component, Fosinoprilat **9**.[31,32]

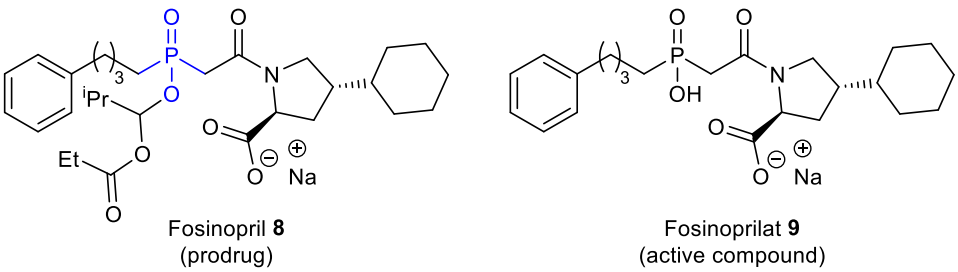
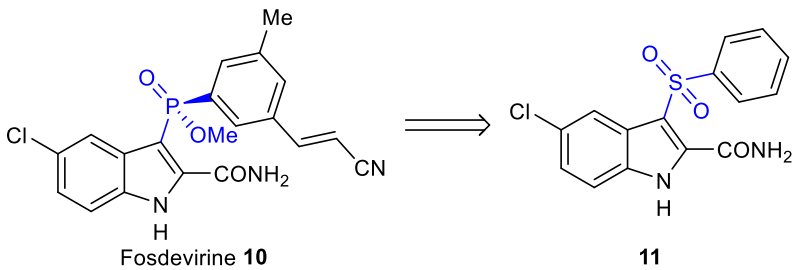


Figure 6: *The structures of phosphinate Fosinopril **8** and its active component **9**.*

A more relevant example to our study is the *P*-stereogenic methylphosphinate, Fosdevirine **10**, Scheme 2.[33,34] Fosdevirine **10** was developed by GSK and ViiV Healthcare, and reached phase II of clinical trials for the treatment of HIV.[33,34] Unfortunately, during the phase IIb clinical trials its development was discontinued due to reports of seizures in the patients.[32] Nevertheless, Fosdevirine **10** is still highly relevant to this report because it is a rare example in industry of a methylphosphinate used as a replacement for a sulfone group.

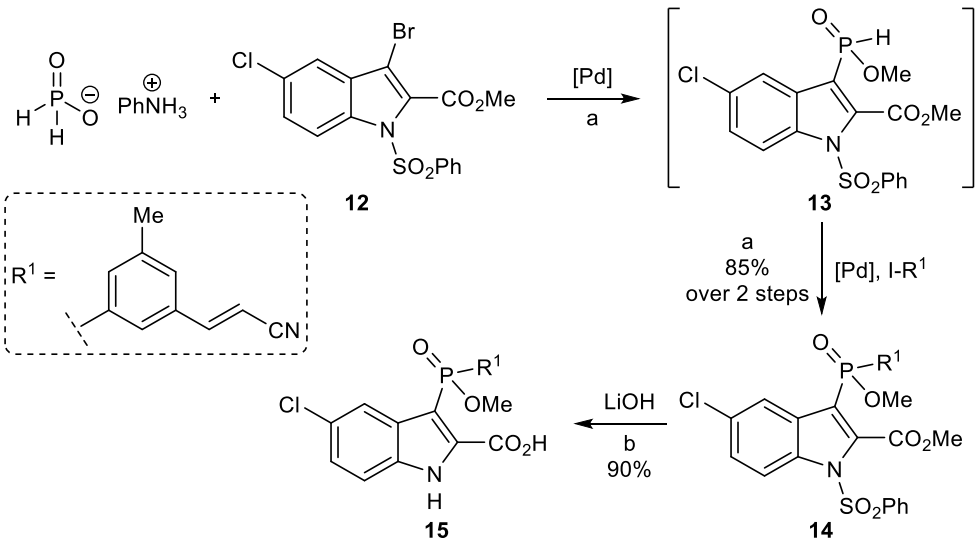


Scheme 2: *Indole-based drugs Fosdevirine **10** and **11**.*

In 1993, Merck Research Laboratories had reported the development of HIV-1 inhibitor **11**, Scheme 2.[35] Although, there were structural changes to the connecting aryl ring, it is clear to see that the phosphinate of **10** was used as a replacement for the sulfone functional group in **11**, Scheme 2. To the best of my knowledge, this is the first reported example of such a replacement. Both Fosdevirine **10** and **11** were designed to affect the same pharmacological target and therefore this could be considered the first example of a methylphosphinates acting as a bioisostere for the sulfone group.

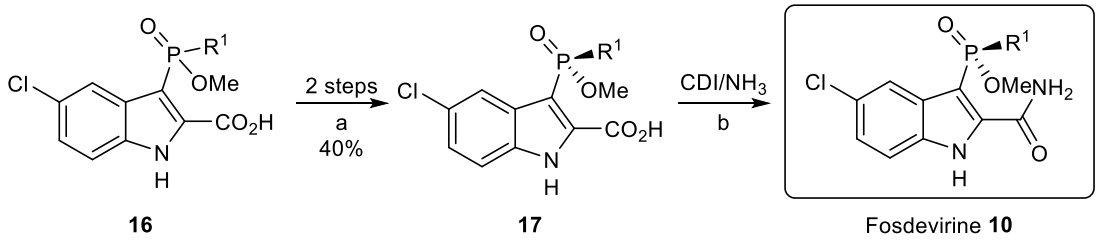
1.3.3. The Synthesis of Fosedevirine **10**

The synthesis of Fosdevirine **10**, outlined a literature route to a methylphosphinate which avoided PCl_3 derived starting materials, Scheme 3.



Scheme 3: *The synthesis of Fosedevirine **10** as developed by GSK and ViiV Healthcare. Reagents and conditions: a)i) aminopropyltrimethoxysilane, toluene r.t., 0.5 h. ii) **12**, $Pd(dppf)Cl_2$, 77 – 82 °C, 1.5 h. iii)R^1-I, $Pd(dppf)Cl_2$, K_2CO_3, 75 °C, 2 h. b) $LiOH•H_2O$, $MeCN/H_2O$, r.t., 2 h.*

The synthesis began with the palladium-catalysed arylation between anilinium hypophosphite and functionalised indole **12**.[33] The one-pot cross-coupling and methylation reaction developed by Montchamp and co-workers, was used and gave *H*-phosphinate **13**. The resulting *H*-phosphinate **13** was not isolated; instead it was converted to the corresponding secondary phosphinate **14** *via* a second cross-coupling reaction. Over the two steps, methylphosphinate **14** was synthesised in 85% yield, Scheme 3. Next, the simultaneous hydrolysis of the sulfonamide and the methyl ester gave compound **15** in 90% yield. The *R*-enantiomer **17** was separated in 40% over a two-step process using cinchonidine, Scheme 4.

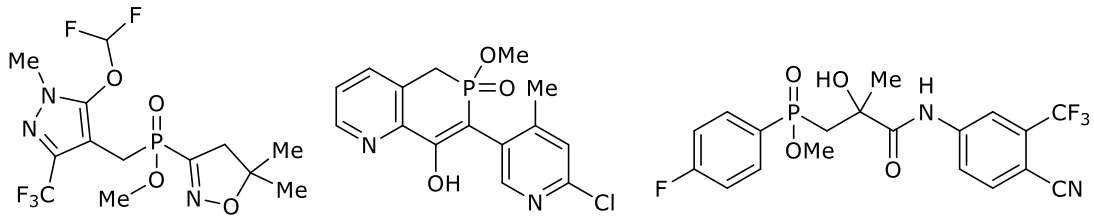


Scheme 4: *The continued synthesis of Fosdevirine **10**. Reagents and conditions: a)i) cinchonidine, **16**, EtOAc, 50 °C, 2 h, r.t., 2 h. ii) HCl (0.1 M aqueous solution), (the process was repeated twice followed by a crystallisation in n-heptane). b)i) CDI, THF. ii) NH_3. iii) MeOH/H_2O.*

The final step of the synthesis was the amide coupling reaction with CDI and ammonia which gave the desired *P*-stereogenic methylphosphinate **10**. Encouraged by the synthesis and existence of Fosdevirine **10**, as well as the general similarities between sulfones and phosphinates (*see section 1.3.1.)*, we wanted to further develop the idea that methylphosphinates could be general replacements for the sulfone group.

1.4. Project Aims

The aim of the project was to investigate whether *P*-stereogenic methylphosphinates were viable bioisosteric replacements for the sulfone functional group. The strategy for the investigation was to synthesise novel phosphinate analogues of known sulfone agrochemical and pharmaceutical compounds. All the syntheses would use hypophosphite derived starting materials, and use methods described in Part 1 where appropriate. A comparison was to be made between phosphinates and their sulfone counterparts, based on the biological activity, potency and/or physical chemistry properties of each compound. The original synthetic targets of this project are seen in Figure 7. The targets are phosphinate analogues of pyroxysulfone **6**, 4-HPPD inhibitor **7** and Casodex® **3**.



18 **19** **20**

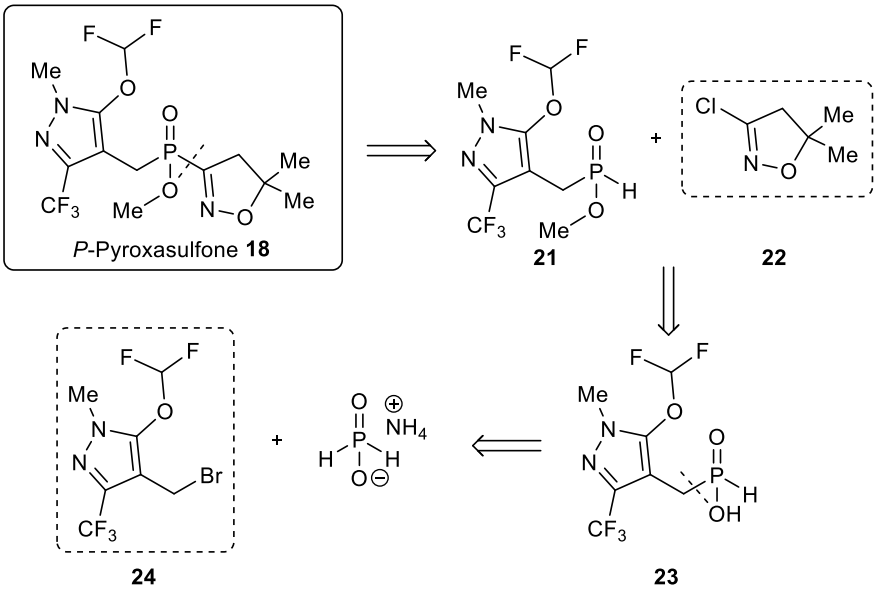
Figure 7: *The phosphinate targets of this project.*

Chapter 2 – Results and Discussion

2.1. *P*-Analogue of Pyroxasulfone

2.1.1. Synthesis Plan

The initial target for this investigation was the methylphosphinate analogue of herbicide pyroxasulfone **18**, Scheme 5. A retrosynthetic analysis of **18** revealed that the *H*-phosphinate fragment **21** could be synthesised *via* a *P*-*C* bond disconnection, Scheme 5.



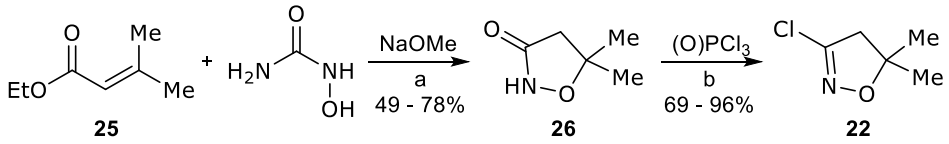
Scheme 5: *The structure and the retrosynthesis of P-pyroxasulfone **18**.*

It was envisaged that this bond could be constructed *via* the deprotonation of *H*-phosphinate **21** and subsequent alkylation with chloroisoxazoline **22**. It was reasoned that the methylation of primary phosphinic acid **23** could synthesise the *H*-phosphinate fragment **21**. Finally, it was expected that phosphinic acid **23** could be formed *via* a *P*-*C* bond formation reaction between functionalised pyrazole **24** and ammonium hypophosphite. For the synthesis of *P*-pyroxasulfone **18**, both

chloroisoxazoline **22** and pyrazole **24** were supplied by Syngenta but could be synthesised by the following literature procedures.

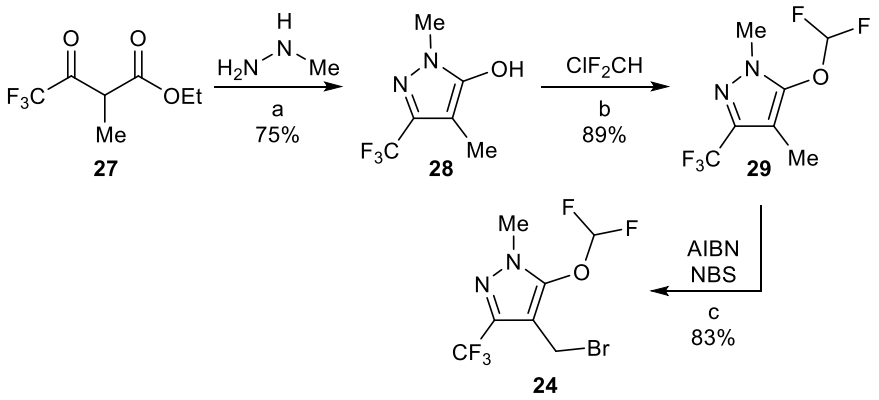
2.1.2. Literature Procedures to Synthesise **22** and **24**

The most convenient synthesis of chloroisoxazoline **22** involved only two steps and was reported by Syngenta in 2007, Scheme 6.[36] Initially, the isoxaolidin-3-one ring **26** was constructed *via* the reaction between hydroxyurea and ethyl 3-methylbut-2-enoate, in the presence of sodium methoxide. The subsequent chlorination of **26**, with $POCl_3$, gave the desired chloroisoxazoline **22** in 34% over two steps. In 2019, Dongguan HecTech R and D Co. Ltd reported the synthesis of chloroisoxazoline **22** in 75% over two steps, using the same synthetic strategy.[37]



Scheme 6: *The literature syntheses of chloroisoxazoline **22**. Reagents and conditions: a)i) Na, MeOH, r.t.. ii) hydroxyurea then* **25**, r.t., 18 h. *b) (O)PCl_3, DMF, CH_2Cl_2, r.t., 2 h.*

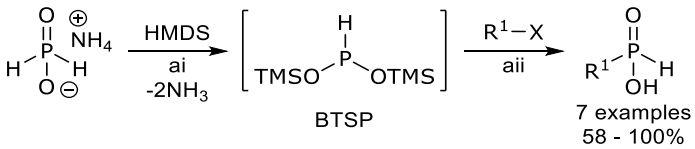
The synthesis of pyrazole-based electrophile **24** was outlined by Nakatani, Ito and Miyazaki, and involved three steps, Scheme 7.[38] The reported synthesis began with the reaction between β-ketoester **27** and methyl hydrazine which constructed the pyrazole ring **28**. The subsequent *O*-alkylation, of **28**, with ClF_2CH and radical bromination at the methyl group of **29**, completed the synthesis of electrophile **24**; an overall yield of 55% was reported.



Scheme 7: *The synthesis of functionalised pyrazole **24**. Reagents and conditions: a) methyl hydrazine, EtOH, <10 °C then r.t., 0.5 h. b) KOH, r.t., ClF_2CH, r.t. – 70 °C, 2 h. c) NBS, AIBN, CCl_4, reflux, 1 h.*

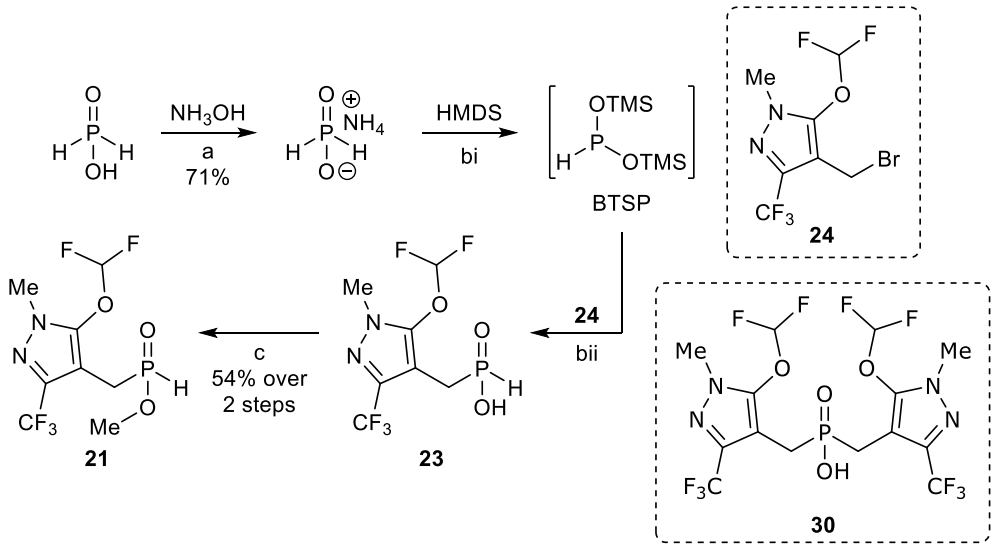
2.1.3. The Synthesis of *H*-Phosphinate **21**

A method to synthesise primary phosphinic acids from ammonium hypophosphite was developed by Boyd and co-workers in 1994.[39] The reported reaction, first, converted ammonium hypophosphite to the nucleophilic bis(trimethylsilyl)phosphonite (BTSP) species *via* a reaction with HMDS. Next, the reaction of BTSP with an appropriate electrophile would form a *P*-*C* bond, and using this method a range of primary phosphinic acids were synthesised, Scheme 8. It was thought that this methodology could be exploited to synthesise the desired primary phosphinic acid **23**.



Scheme 8: *The synthesis of primary phosphinic acids via silyl-phosphonite chemistry developed by Boyd and co-workers. Reagents and conditions: a)i) HMDS, 100 – 110 °C, 1 – 2 h. ii) 0 °C, CH_2Cl_2, R^1-X, r.t., overnight.*

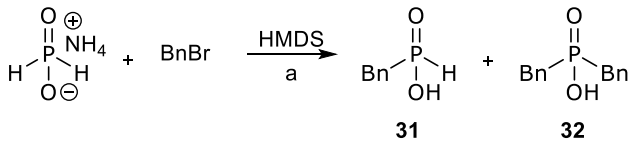
The synthesis of *P*-pyroxasulfone **18** began with formation of ammonium hypophosphite, which was achieved in 71% yield from hypophosphorus acid and ammonium hydroxide, Scheme 9.



Scheme 9: *The synthesis of H-phosphinate fragment **21** via the silyl-phosphonite chemistry developed by Boyd and co-workers. Reagents and conditions: a) hypophosphorus acid (50 wt%. solution in H_2O), ammonium hydroxide (25 wt%. solution in H_2O), 0 °C – r.t., 0.5 h. b)i) HMDS (1.05 eq.), 110 °C, 2 h. ii) **24** (0.20 eq.), CH_2Cl_2, 0 °C - r.t., 16 h. c)i) (trimethylsilyl)diazomethane (4.0 eq., 2.0 M in hexanes), toluene/MeOH (4:1), r.t., 25 min. ii) AcOH (conc.).*

Next, a model substrate was used to test the synthesis of primary phosphinic acids using BTSP and benzyl bromide, Scheme 10. It was found that if a 1:1 ratio of ammonium hypophosphite and benzyl bromide were used, then mixtures of **31** and **32** were obtained. This problem was negated by using 0.2 equivalents of benzyl bromide; therefore during the synthesis of phosphinic acid **23**, ammonium hypophosphite was used in excess (0.20 eq. of **24** with respect to ammonium hypophosphite). The primary phosphinic acid was synthesised and no evidence for the formation of by-product **30** was seen. When performing the *in situ* formation of

BTSP it was also imperative to use a constant flow of argon, to prevent the oxidation of the BTSP.

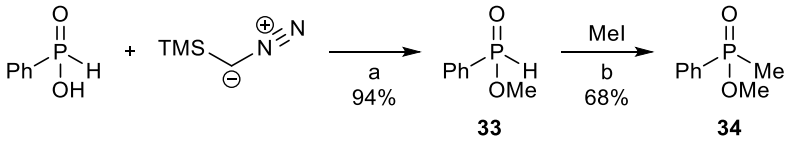


Scheme 10: *Model BTSP alkylation reaction using benzylbromide: Reagents and conditions: a)i) HMDS (1.02 eq.), 100 - 110 °C, 2 h. ii) BnBr (0.200 – 1.02 eq.), CH_2Cl_2, 0 °C – r.t., 16 – 17 h.*

Primary phosphinic acid **23** was synthesised, however, it could not be sufficiently purified at this stage; therefore it was isolated as the methylphosphinate **21**, Scheme 9. The methylation of phosphinic acid **23** was performed with (trimethylsilyl)diazomethane. (Trimethylsilyl)diazomethane was chosen because it is able to selectively methylate the *O-H* bond over the *P-H* bond due to the differences in their acidities. A clean conversion to *H*-phosphinate **21** was achieved and it was synthesised in 54% yield over the two steps, Scheme 9.

2.1.4. The Final *P-C* Bond Formation Reaction

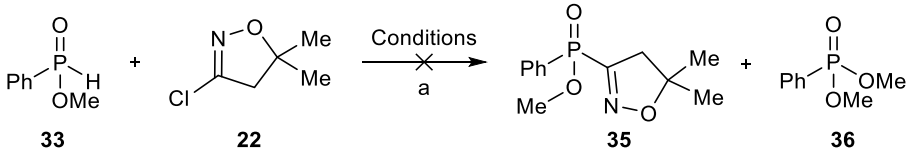
To investigate the final *P-C* bond formation of a *H*-phosphinate, a simple model compound **33**, was synthesised, Scheme 11. The methylation of phenylphosphinic acid with (trimethylsilyl)diazomethane gave *H*-phosphinate **33** in 94% yield. The subsequent methylation of **34** was achieved using sodium hydride at room temperature. For this transformation it was found that sodium hydride was preferable to lithium hexamethyldisilazane (LiHMDS), and the optimised conditions used sodium hydride which had the mineral oil removed. Under these optimised conditions methylphosphinate **34** was synthesised in 68% yield, Scheme 11.



Scheme 11: *The two-step synthesis of methylphosphinate **34**. Reagents and conditions: a) (trimethylsilyl)diazomethane (4.0 eq., 2.0 M in hexanes), toluene/MeOH (4:1), r.t., 1 h. b)i) NaH (1.2 eq., neat), THF, r.t. ii) MeI (3.0 eq.), r.t., 16 h.*

These conditions were applied to the reaction with chloroisoxazoline electrophile **22**. Although the starting material **33** had been consumed, the desired product was not observed, and **22** remained after the reaction, Table 2 Entry 1. Other conditions were attempted but with no success.

Table 2: *The attempted synthesis of methylphosphinate **31**.*



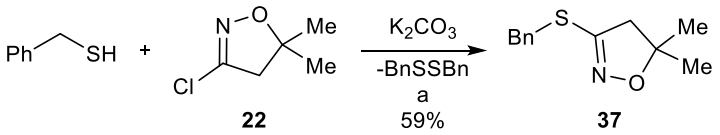
Entry	Base	Solvent	Temp. / °C	Yield **35** %
1[b]	NaH	THF	r.t.	0
2	NaH	THF	r.t.	0
3[c]	NaH	THF	r.t	0
4	NaH	THF	50	0
5	NaH	THF	70	0
6	NaH	DMF	r.t.	0

Reagents and conditions: a) base (1.2 eq.), solvent, temp., 1 – 18 h. b) NaH (neat) was used. c) 15-crown-5 was used.

A crown ether (15-crown-5) was used in an attempt to increase the nucleophilicity of the phosphinate anion, Table 2 Entry 3. Even with increased temperatures no product was observed. Furthermore, the reaction was still unsuccessful with a change of solvent, Table 2 Entry 4 - 6. During the reaction with chloroisoxazoline **22** a completely unexpected species, phenyldimethylphosphonate **36**, was formed. The

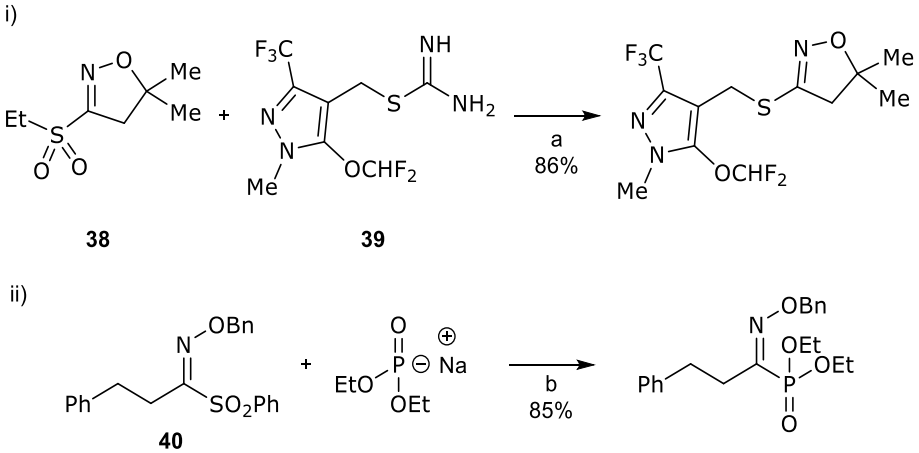
mechanism for this transformation was unknown and additional reactions would need to be performed to investigate the formation of phosphonate **36**.

During the synthesis of the original pyroxasulfone compound **6** and its derivatives, various sulfur-based nucleophiles were reported to successfully react with chloroisoxazoline **22** at room temperature.[38,40] To replicate such a transformation, a simple sulfur nucleophile, benzyl mercaptan, was reacted with chloroisoxazoline **22** and the desired product **37** was synthesised in 59% yield, Scheme 12.[40]



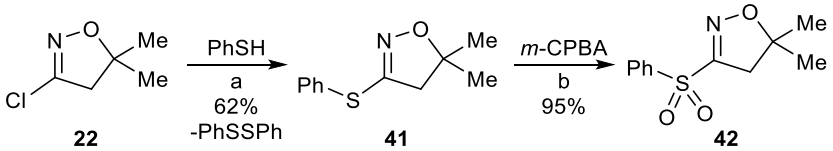
Scheme 12: *The addition of benzyl mercaptan with chloroisoxazoline **22**. Reagents and conditions: a) K_2CO_3 (6.5 eq.), DMF, r.t., 5 h.*

If a sulfur nucleophile could successfully react with chloroisoxazoline **22** then it was clear that, in our example, the *H*-phosphinate and **22** were not compatible. After consulting the literature it was decided to adapt the isoxazoline electrophile.



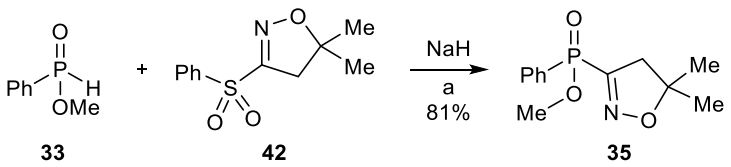
Scheme 13: *i) An example of a sulfone-based isoxazoline **38** being used during the synthesis of pyroxasulfone. ii) The addition of sodium diethylphosphonate to sulfonyl oxime ether **40**, as reported by Kim and co-workers. Reagents and conditions: a)i) **38**, K_2CO_3, H_2O, r.t., 0.5 h ii) **39**, DMF, K_2CO_3, r.t. – 50 °C, 3 h. b) THF, – 78 °C.*

Some syntheses of pyroxasulfone described the use of ethylsulfone **38** instead of chloroisoxazoline **22**. One example demonstrated the coupling between carbamimidothioate **39** and ethylsulfone **38**, under basic conditions, to give the reduced version of pyroxasulfone, Scheme 13i.[38] Furthermore, in 2010, Kim and co-workers reported the general nucleophilic substitution at sulfonyl oxime ethers with a variety of nucelophiles.[41] The successful addition of sodium diethylphosphonate to oxime ether **40** was also described, Scheme 13ii.[41] In order to replicate this reaction, phenylsulfone **42** first needed to be synthesised.



Scheme 14: *The two step synthesis of sulfone **39**. Reagents and conditions: a) PhSH (6.2 eq.), K_2CO_3, DMF, r.t., 4 days. B) m-CPBA (70%, 2.5 eq.), CH_2Cl_2, r.t., 24 h.*

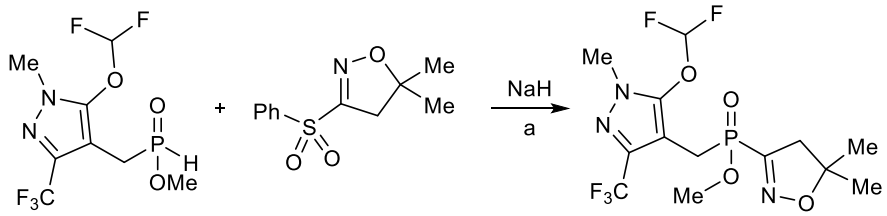
Initially the addition of 1.0 equivalents of thiophenol to chloroisoxazoline **22** gave the desired thioether **41** in a 22% yield. It was reasoned that the thiophenol was being consumed *via* a competitive oxidative coupling reaction to form phenyl disulfide. A much improved yield of 62% was achieved with 6.20 equivalents of thiophenol, Scheme 14. The subsequent oxidation of thioether **41** with *m*-CPBA gave sulfone **42** in 95% yield, Scheme 14. Employing the conditions developed by Kim and co-workers, the reaction between sulfone isoxazoline **42** and methylphosphinate **33** was attempted, and the desired product **35** was isolated in 81%, Scheme 15.



Scheme 15: *The synthesis of **35**. Reagents and conditions: a)i) **33** (1.5 eq.), NaH (1.65 eq., neat), THF, r.t. - –78 °C ii) **42** (1.0 eq.), – 78 °C – r.t., 20 h.*

Next, the reaction was to be attempted with phosphinate **21**, Table 3. Although the desired *P*-pyroxasulfone **18** was observed, it could not be isolated, Table 3 Entry 1. Instead an inseparable mixture of **21** and **18** was isolated. Initially, an excess of **21** was used during the reaction to ensure full consumption of isoxazoline **42**, but in light of this result the reaction conditions were optimised.

Table 3: *The synthesis of P-pyroxasulfone **18**.*



21 **42** **18**

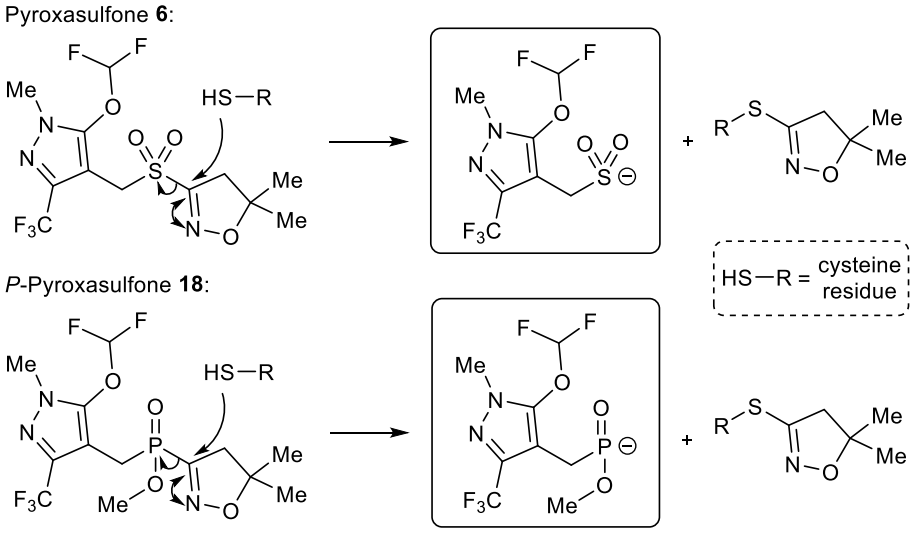
Entry	**21** / eq.	**42** / eq.	NaH / eq.	Temp. / °C	Time / h	Yield / %
1	1.50	1.00	1.65	–78 - r.t.	20	-
2	1.00	1.50	1.20	–78	2	15
3[b,c]	1.00	1.50	1.10[d]	–78 - – 40	1	31
4[b,c]	1.00	1.50	1.10	–78 - – 40	3	67

*Reagents and conditions: a) **21** (eq.), **42** (eq.), NaH (eq., neat), temp., time. b) both **21** and **42** were present during the addition of NaH. c) NaH was added batch-wise at – 78 °C. d) NaH (0.20 eq., neat), added after 0.5 h.*

To ensure full consumption of phosphinate **21**, 1.5 equivalents of isoxazoline **42** were used, Table 3 Entry 2. Even though the only phosphorus species present in the crude reaction mixture was the desired product **18** the isolated yield was still low. It was clear that *H*-phosphinate **21** was decomposing *via* an unknown pathway. To combat this, the phosphinate anion was generated in the presence of the electrophile **42**, to encourage its alkylation instead of any decomposition pathways, Table 3 Entry 3 and 4. When the reaction was held at – 40 °C for 3 h, with no further addition of sodium hydride, the desired product was isolated in 67% yield, Table 3 Entry 4.

2.1.5. Conclusion

P-pyroxasulfone **18** was synthesised in 26% yield over six steps from intermediates **22** and **24**. It was subsequently tested for pre-emergence herbicidal activity but unfortunately the phosphorus analogue of pyroxasulfone was inactive. Pyroxasulfone **6** is a covalent inhibitor of VLCFAE (*see Section 1.2.2.*) and therefore relies on the sulfone moiety to act as a leaving group, Scheme 16.



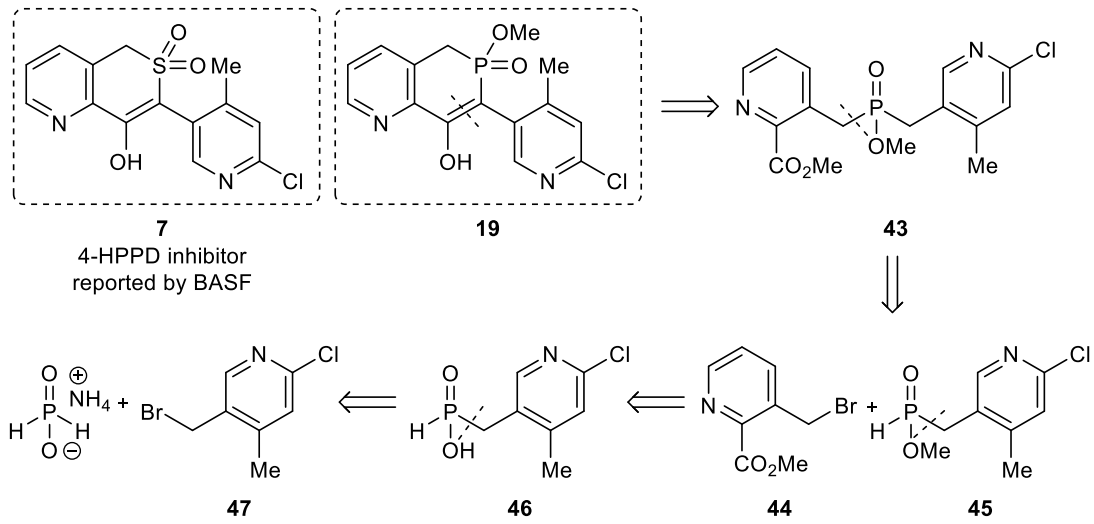
Scheme 16: *A comparison between the mode of action of and pyroxasulfone **18**.*

Evidently exchanging the sulfone moiety for a methylphosphinate functional group is detrimental to its ability to inhibit the VLCFAE. It was therefore hypothesised that, when compared to the sulfone, the methylphosphinate was not a capable leaving group. It was further reasoned that sulfone functional group is more electron withdrawing than the phosphinate, and is better at stabilising the derived anion. In conclusion, *P*-pyroxasulfone was successfully synthesised in moderate yields but was unsuccessful at acting as a bioisostere for the original sulfone-based pyroxasulfone. Next, to continue the investigation phosphinate analogues of sulfone herbicides with an alternative mode of action were to be synthesised.

2.2. The Synthesis of Phosphinate 19

2.2.1. Retrosynthetic Analysis

The second target in the investigation was methylphosphinate **19**, which is an analogue of the 4-HPPD inhibitor reported by BASF, Scheme 17.[26] Similar to the synthesis of the original sulfone herbicide, it was envisaged that the final *C*-*C* bond could be constructed *via* a 6-*exo*-*trig* cyclisation reaction, Scheme 17.[26]

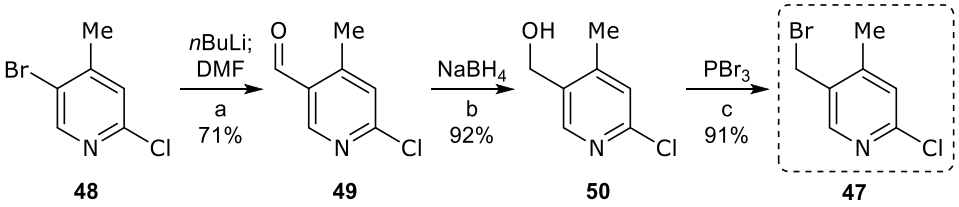


Scheme 17: *The retrosynthetic analysis of cyclic phosphinate **43**.*

It was reasoned that the desired acyclic phosphinate precursor **43** could be synthesised *via* a similar strategy to that employed for the synthesis of *P*-pyroxasulfone **18**. Two further *P*-*C* bond disconnections would lead to pyridine-based electrophiles **47** and **44**, and ammonium hypophosphite. It was expected that the first *P*-*C* bond could be formed by the silyl-phosphonite chemistry developed by Boyd *et. al.*, and then the subsequent alkylation of *H*-phosphonite with picolinate **44** could construct the second *P*-*C* bond.

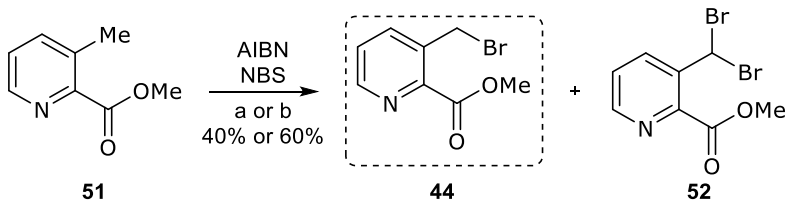
2.2.2. The Synthesis of Electrophiles **44** and **47**

Pyridine-based electrophiles **44** and **47** were key for the formation of the desired *P-C* bonds. Electrophile **47** was synthesised in three steps from commercially available 5-bromo-2-chloro-4-methylpyridine **48**, Scheme 18. A selective lithium-halogen exchange, at the bromine, followed by the addition of DMF and quenching with NH_4Cl gave aldehyde **49** in 71% yield. The subsequent reduction with sodium borohydride and bromination with phosphorus tribromide gave the desired 5-bromomethyl-2-chloro-4-methylpyridine electrophile **47**, in 84% over the two steps.



Scheme 18: *The three-step synthesis of **47** Reagents and conditions: a)i) n-BuLi (1.0 eq., 2.0 M in hexanes), Et_2O, – 78 °C, 0.75 h. ii) DMF (1.4 eq.), – 78 °C, 1.5 h. iii) sat.NH_4Cl. b) $NaBH_4$ (0.50 eq.), MeOH, 0 °C – r.t., 1 h. c) PBr_3 (1.5 eq.), CH_2Cl_2, 0 °C – r.t., 2 h.*

The second electrophile **44** was synthesised in one step from methyl 3-methylpicolinate **51** *via* a radical bromination with AIBN and NBS, Scheme 19. Both benzene and trifluorotoluene were suitable solvents in this reaction, and **44** was obtained with of 60% and 40%, respectively.

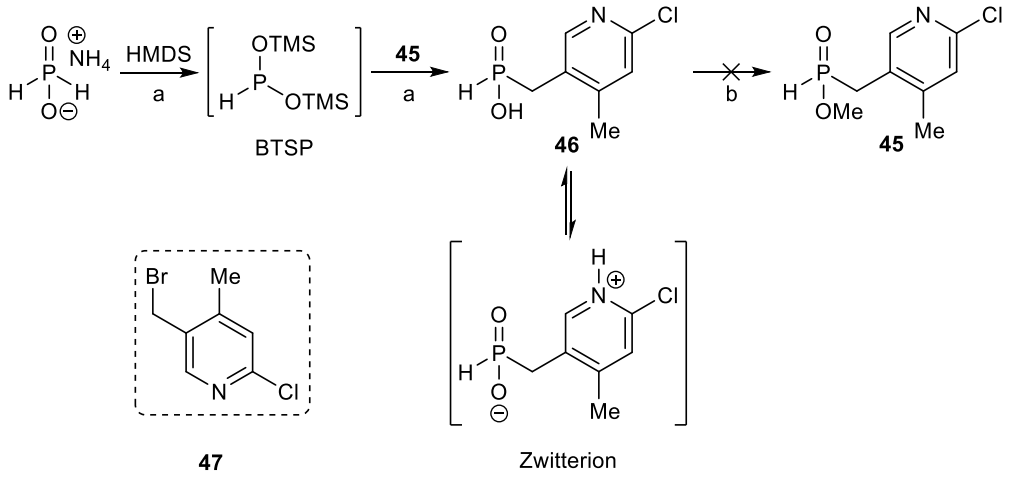


Scheme 19: *The radical bromination reaction to form **44**. Reagents and conditions: a) NBS (0.50 eq.), AIBN (5.0 mol%), trifluorotoluene, 85 °C, 1 h, (repeated three times). b) NBS (0.50 eq.), AIBN (5.0 mol%), benzene, 85 °C, 2 h, (repeated twice).*

Although benzene gave **44** in a superior yield, on a large scale trifluorotoluene was preferred because it is not carcinogenic. The remainder of the mass balance in the bromination reaction was accounted for by unreacted starting material **51** the unwanted dibromide **52**, Scheme 19.

2.2.3. Construction of the Key *P-C* Bonds

It was thought that *H*-phosphinate **45** could be synthesised *via* the methylation of phosphinic acid **46**, which in turn could be synthesised by the monoalkylation of BTSP with **47**, Scheme 20.[39] However, it was soon realised that the phosphinic acid **46** was completely aqueous soluble because it existed in equilibrium with its zwitterionic complex, Scheme 20.

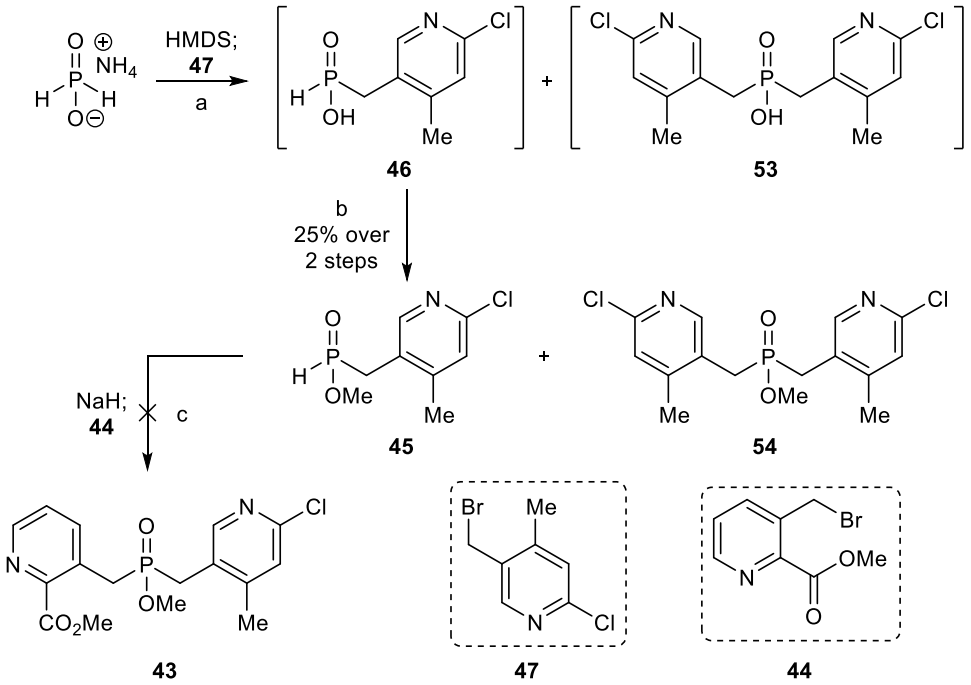


Scheme 20: *Attempted synthesis of H-phosphinate **45** Reagents and conditions: a)i) HMDS (1.05 eq.), 110 °C, 2 h. ii) 0 °C, **47** (0.20 eq.), CH_2Cl_2, r.t., 16 h. b) (trimethylsilyl)diazomethane (1.0 eq., 2.0 M in hexanes), toluene/MeOH (4:1), r.t., 0.5 h.*

For this reason the compound could not be purified by an acid/base work-up. When the electrophile **47** was undercharged (0.20 eq. with respect to ammonium hypophosphite) to avoid over-alkylation, excess hypophosphorus acid remained and could not be removed. Although the desired product was observed, it could not be

isolated. Even the direct methylation of the crude material was unsuccessful, presumably due to the presence of the hypophosphorus acid.

In an attempt to consume all the BTSP during the synthesis of primary phosphinic acid **46**, a 1:1 ratio of electrophile **47** to ammonium hypophosphite was used, Scheme 21.

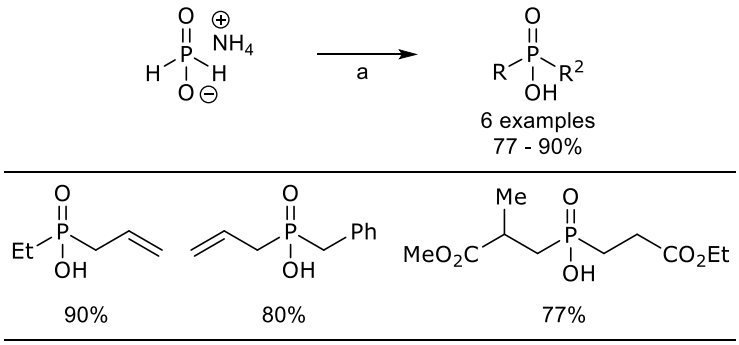


Scheme 21: *The attempted synthesis of secondary phosphinate **43** Reagents and conditions: a)i) HMDS (1.05 eq.), 110 °C, 2 h. ii) 0 °C, **47** (1.0 eq.), CH_2Cl_2, r.t., 18 h. b)* (trimethylsilyl)diazomethane (3.2 eq., 2.0 M in hexanes), toluene/MeOH (4:1), r.t., 0.5 h. c) NaH *(1.1 eq.), **44** (1.0 – 1.5 eq.), THF, – 78 °C – r.t..*

Fortunately, the desired primary phosphinic acid **46** was the major species by ^{31}P NMR spectroscopy, Scheme 21. The subsequent methylation of the crude material using (trimethylsilyl)diazomethane gave *H*-phosphinate **45** in 25% yield, Scheme 21. During the synthesis of **45**, there was evidence to suggest that small quantities of quantities of **53** were formed. The following alkylation of *H*-phosphinate **45** with electrophile **47** was unsuccessful. Sodium hydride was employed as the base and reactions were carried out at temperatures ranging from – 78 °C to room

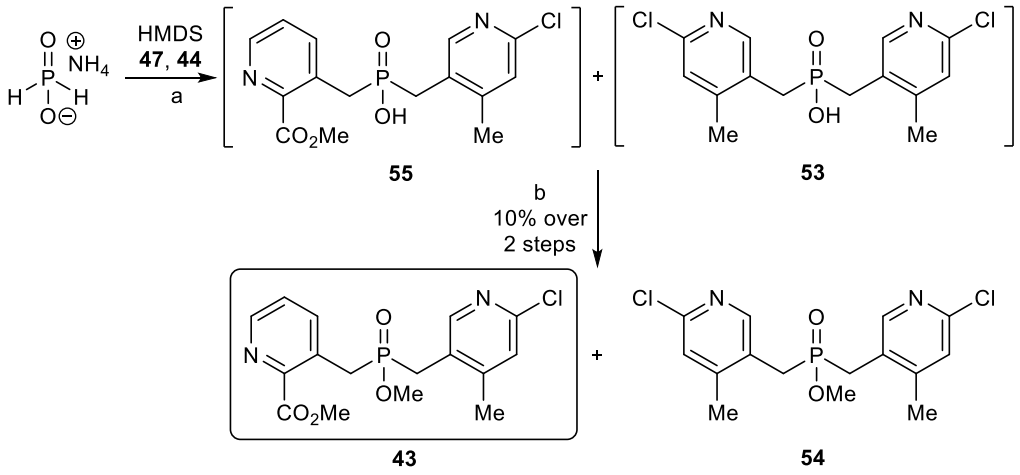
temperature. Both unreacted **45** and **47** remained in significant quantities and only negligible amounts of the desired product **44** was observed by ^{31}P NMR spectroscopy, therefore an alternative strategy was attempted.

An extension of the silyl-phosphonite chemistry developed by Boyd and co-workers encompassed the synthesis of unsymmetrical secondary phosphinic acids in a one-pot manner, Scheme 22.[39,42] Both alkyl and acrylate electrophiles were employed and the yields of the reaction were between 77 – 90%.



Scheme 22: The synthesis of unsymmetrical phosphinic acids developed by Boyd *et. al.:* a*)i) HMDS, 100 – 110 °C, 1 – 2 h. ii) electrophile, CH_2Cl_2, 0 °C – r.t., 16 h. iii) electrophile, CH_2Cl_2, 0 °C – r.t., 16 h. iv) HMDS, 0 °C, 2 h v) second electrophile, 0 °C – r.t., 16 h*.

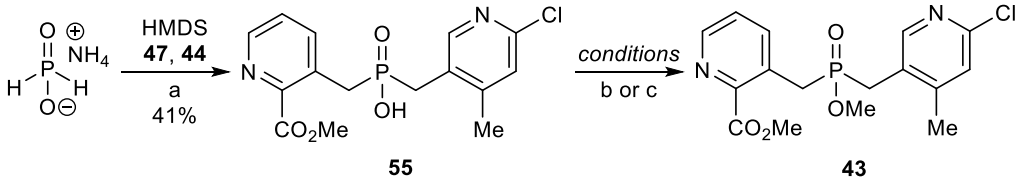
This approach looked suitable for the formation of **43** therefore the one-pot synthesis of the secondary phosphinic acid was attempted. Following the procedure outlined by Boyd and co-workers, the desired species was observed by ^{31}P NMR spectroscopy but could not be isolated. Instead the corresponding methylphosphinate **43** was synthesised in 10% yield over the two steps, Scheme 23. Although the yield was low it has to be considered that three new bonds had been formed during a very complex reaction. There was also evidence to suggest that by-product **53** and **54** were formed during this process.



Scheme 23: *Telescoped synthesis of secondary phosphinate **43** over two steps from ammonium hypophosphite. Reagents and conditions: a)i) HMDS (1.0 eq.), 110 °C, 2 h. ii) 0°C, CH_2Cl_2, **45** (1.0 eq.), r.t. 16 h. iii) 0 °C, HMDS (1.0 eq.), 2 h. iv) 0 °C, **43**, CH_2Cl_2, r.t., 21 h. v) MeOH, r.t.. b) (trimethylsilyl)diazomethane (2.0 eq., 2.0 M in hexanes), toluene/ MeOH (4:1), r.t., 0.5 h.*

Following on from this synthesis, it was later found that phosphinic acid **55** could be purified by reverse-phase column chromatography, and was isolated in 41% yield, Table 4. An alternative methylation with methyl iodide was attempted with the pure material and gave the corresponding methylphosphinate **43** in 65% yield, Table 4 Entry 3. It was found that when pure phosphinic acid **55** was used, the methylation with methyl iodide produced higher yields compared to using (trimethylsilyl)diazomethane, with 41 being obtained in 27% over the two steps, Table 4 Entry 3.

Table 4: *The synthesis of **43** from purified phosphinic acid **55**.*



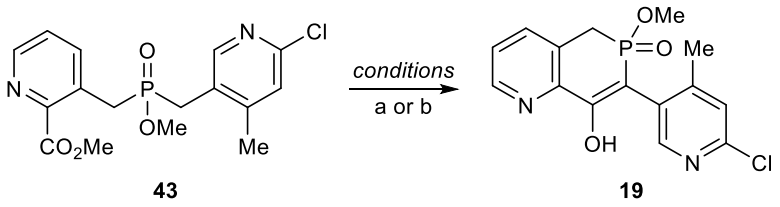
Entry	**55**	Methylating agent	Yield for methylation / %	Yield over 2 steps / %
1[b]	Crude	(trimethylsilyl) diazomethane	-	10
2[b]	Pure	(trimethylsilyl) diazomethane	50	21
3[c]	Pure	MeI / Cs_2CO_3	65	27

*Reagents and conditions: a)i) HMDS (1.0 eq.), 110 °C, 2 h. ii) 0°C, CH_2Cl_2, **47** (1.0 eq.), r.t. 18 h. iii) 0 °C, HMDS, 2 h. iv) 0 °C, **44**, CH_2Cl_2, r.t., 18 h. v) MeOH, r.t.. b) (trimethylsilyl)diazomethane (2.0 eq., 2.0 M in hexanes), toluene/ MeOH (4:1), 0 °C - r.t., 0.5 h. c) MeI (1.6 eq), Cs_2CO_3 (2.0 eq.), MeCN, 40 °C, 1 h, 50 °C, 6.25 h, MeI (0.50 eq.), 50 °C, 2 h.*

2.2.4. The Cyclisation Step

The final step for the synthesis of cyclic phosphinate **19** was the 6-*exo-trig* cyclisation of the corresponding methylphosphinate **43**. A couple of different reaction conditions were attempted, but the highest yielding conditions were those described by BASF for the synthesis of the original sulfone herbicide **7**, Table 5 Entry 2.[26] For this reaction methylphosphinate **43** was heated to 60 °C in the presence of DBU for 24 h, and the desired cyclic product **19** was isolated in 47% yield, Table 5 Entry 2. When the reaction with DBU was monitored by LC-MS, it suggested that the reaction was proceeding cleanly to the desired product, but full conversion was not achieved. Nevertheless, it was found that the purification method used for isolation of **19** had a significant impact on the yield. Recrystallisation of **19** was preferred over column chromatography, and the optimal recrystallisation solvent for the purification of **19** was MeCN.

Table 5: *The final step cyclisation to synthesise cyclic phosphinate **19**.*

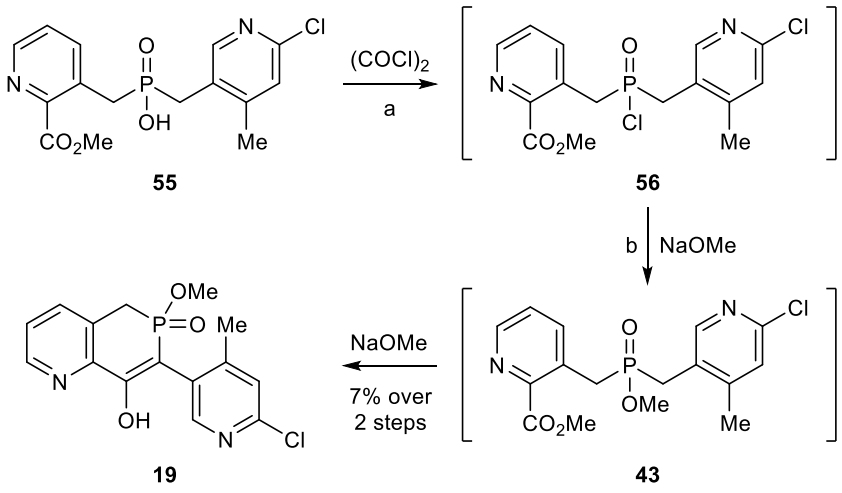


43 **19**

Entry	Base	Solvent	Temp. / °C	Time / h	Yield / %
1[a]	NaOEt	EtOH	r.t.	3	33
2[b]	DBU	MeCN	60	24	47

Reagents and conditions: a) NaOEt (2.0 eq., 21 wt% in EtOH), EtOH, r.t., 3 h. b) DBU (2.5 eq.), MeCN, 60 °C, 24 h.

An alternative synthesis of cyclic phosphinate **19** was attempted directly from phosphinic acid **55**, Scheme 24. It was envisaged that phosphinic acid **55** could be converted to the corresponding phosphinic chloride **56** *via* chlorination with oxalyl chloride. Then the subsequent addition of excess sodium methoxide could not only form the methylphosphinate **43**, but could promote the final cyclisation to **19**.



55 **56** **19** **43**

Scheme 24: *The attempted synthesis of cyclic phosphinate **19** from primary phosphinic acid **55**. Reagents and conditions: a) $(COCl)_2$ (1.1 eq.), CH_2Cl_2, r.t., 0.5 h. b) NaOMe (3.0 eq., 25 wt% in MeOH), MeOH, 0 °C – r.t., 16h.*

The idea was tested but the desired product was only isolated in 7% yield, therefore this route was not deemed a viable option for the synthesis of cyclic phosphinate **19**. The optimum route to **19** was *via* the isolation of methylphosphinate **43** and subsequent cyclisation with DBU, Table 5.

2.2.5. Cyclic Phosphinate **19**

The final compound **19** was synthesised in 8% yield over 7 steps and it was found that the highlighted phosphorus-containing ring is unprecedented. Compound **19** was isolated as a 1.3:1 mixture of atropisomers. It was reasoned the restricted rotation about the highlighted *C*-*C* bond was responsible for this, Figure 8. The x-ray structure was obtained and it showed the presence of a *H*-bond between N16 and O22, locking **19** as the enol tautomer, Figure 8.

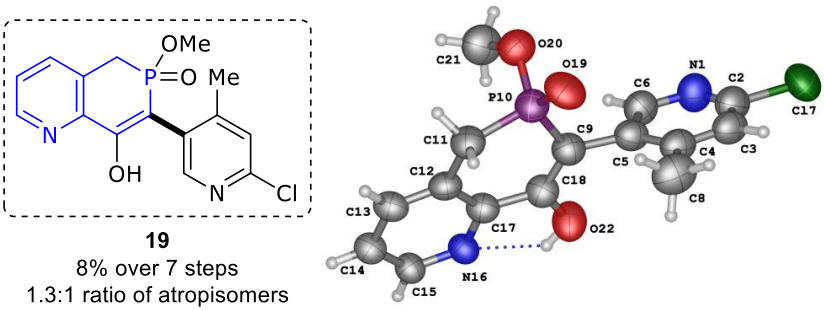


Figure 8: *The X-ray crystal structure of* **19**.

Variable temperature NMR studies were performed on **19**, Figure 9. In the ^{31}P NMR spectroscopy experiment, it was found that when the sample was heated to 90 °C, the two phosphorus peaks coalesced into one broad signal. Moreover, a similar scenario can be observed in the ^{1}H NMR spectra. The magnified region shows the two doublets which correspond to the two methyl peaks for each atropisomer. Again it can be observed that at 90 °C, these two doublets coalesce to single doublet, Figure 9. It was also important to show that when the sample was returned to room

temperature, the ratio of isomers was unchanged, demonstrating that the sample had not been permanently altered. These observations further support the hypothesis that **19** exists as a mixture of atropisomers.

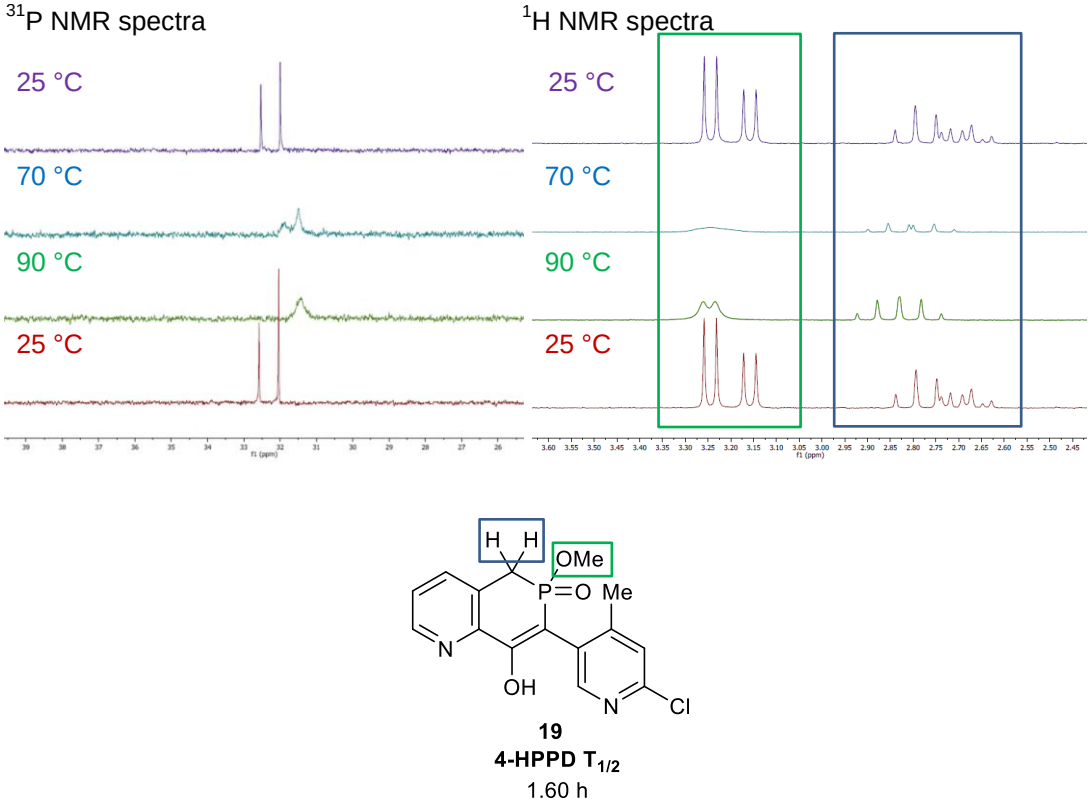


Figure 9: *The ^{31}P and ^{1}H NMR variable temperature experiments for **19**.*

Unfortunately phosphinate **19** was found to be inactive as a 4-HPPD inhibitor during the glasshouse tests. However, it did show low binding to 4-HPPD during the HPPD off-rate assay, Figure 9. Encouraged by this, further analogues of **19**, compounds **56** and **57**, were to be synthesised, Scheme 10.

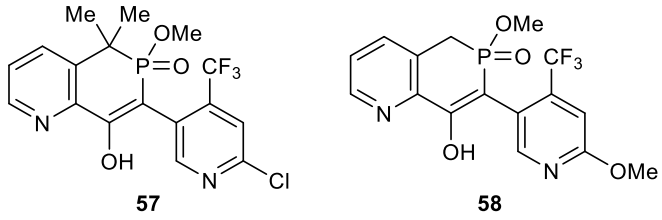
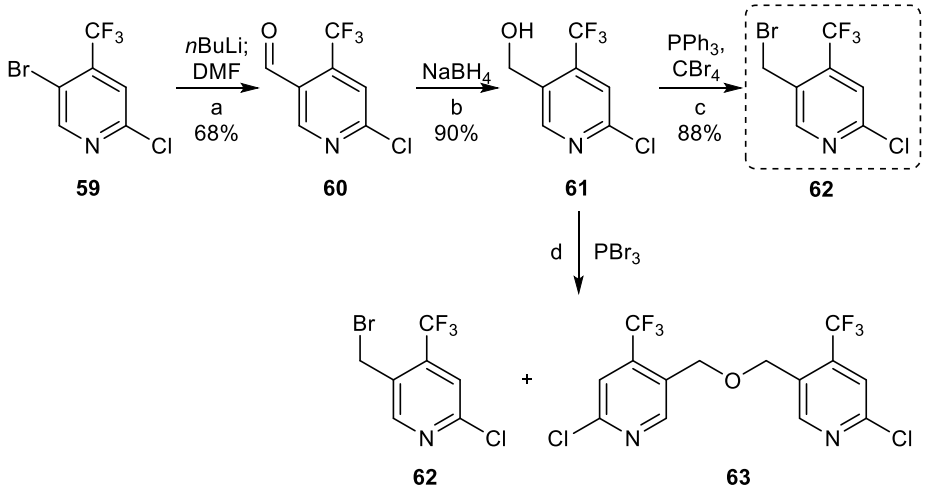


Figure 10: *The alternative phosphinate analogues **57** and **58**.*

2.3. Alternative Analogues 57 and 58

2.3.1. The Synthesis of **57**

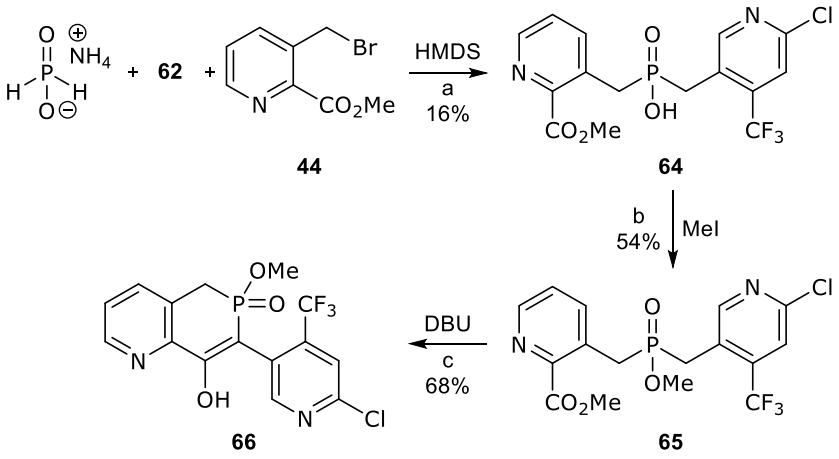
The syntheses of the new analogues were completed by adapting the route used to prepare the original cyclic phosphinate **19**. The formation of the aldehyde **60** and subsequent reduction proceeded as expected, and the desired alcohol **61** was isolated in 61% yield over the two steps, Scheme 25.



Scheme 25: *The synthesis of pyridine based-electrophile **62**. Reagents and conditions: a) a)i) n-BuLi (1.0 eq., 2.0 M in hexanes), Et_2O, – 78 °C, 0.75 h ii) DMF (1.7 eq.), – 78 °C, 1.5 h iii) sat.NH_4Cl b) $NaBH_4$ (0.50 eq.), MeOH, 0 °C – r.t., 1 h. c) PPh_3 (1.2 eq.), CBr_4 (1.2 eq.), CH_2Cl_2, 0 °C – r.t., 2 h. d) PBr_3 (1.5 eq.), CH_2Cl_2, 0 °C – r.t., 2 – 16 h.*

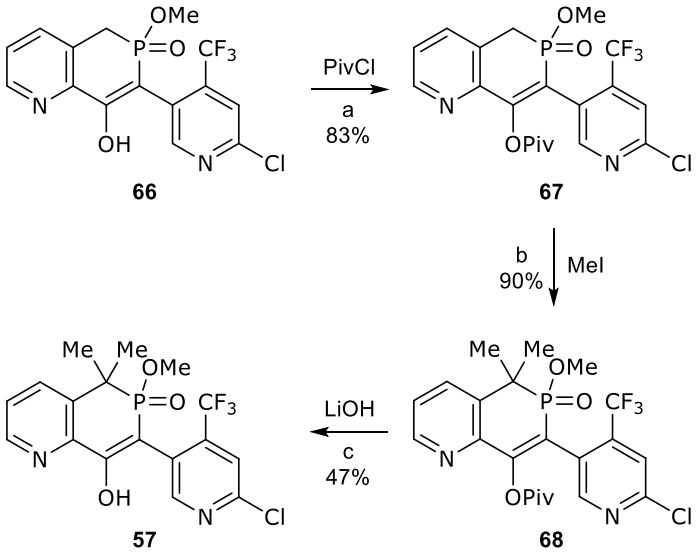
Unexpectedly, the bromination of **61** with PBr_3 was unsuccessful. Instead, an inseparable mixture of the desired product **62** and another species was isolated in a ratio of 1:1.1, respectively, Scheme 25. The unwanted by-product was suspected to be symmetrical ether **63** but this could not be confirmed. It was reasoned that it would form *via* the nucleophilic attack of the alcohol starting material **61** with the product **62**. The problem was solved by performing an Appel reaction with PPh_3 and CBr_4. The desired product **62** was isolated in 88% yield, with no evidence for the formation of **63**, Scheme 25. The remainder of the synthesis proceeded as depicted in Scheme 26, with the cyclic phosphinate **66** being isolated in 6% yield over the

next three steps, Scheme 26. When secondary phosphinic acid **64** could not be isolated *via* reverse phase column chromatography, acyclic methylphosphinate **65** could be obtained in 14% from ammonium hypophosphite, following an alternative telescoped synthesis.



Scheme 26: *The synthesis of cyclic phosphinate **66**. Reagents and conditions: a) HMDS (1.0 eq.), 100 - 110 °C, 1.5 h. ii) 0°C, CH_2Cl_2, **62** (1.0 eq.), r.t. 18 h. iii) 0 °C, HMDS (1.0 eq.), 2 h. iv) 0 °C, **44** (1.0 eq.), CH_2Cl_2, r.t., 18 h. v) MeOH, r.t.. b) MeI (1.5 eq.), Cs_2CO_3 (2.0 eq.), MeCN, r.t., 80 °C, 1.25 h. c) DBU (2.5 eq.), MeCN, 60 °C, 16 h.*

The desired geminal dimethyl group, of **57**, was installed over three steps. To avoid any competitive methylation, the alcohol of **66** was protected with a pivaloyl protecting group, Scheme 27. Next, the dimethylation of the α-carbon was achieved *via* an alkylation with methyl iodide and caesium carbonate, Scheme 27. The desired product **68** was isolated in 73% over the two steps. The final deprotection of **68** was performed with lithium hydroxide, and **57** was obtained in 49% yield, Scheme 27. It was suspected a competitive hydrolysis of the methylphosphinate ester was responsible for the low yield. In summary cyclic phosphinate **57** was synthesised in 2% overall yield, and was isolated as a 1:1 mixture of atropisomers.

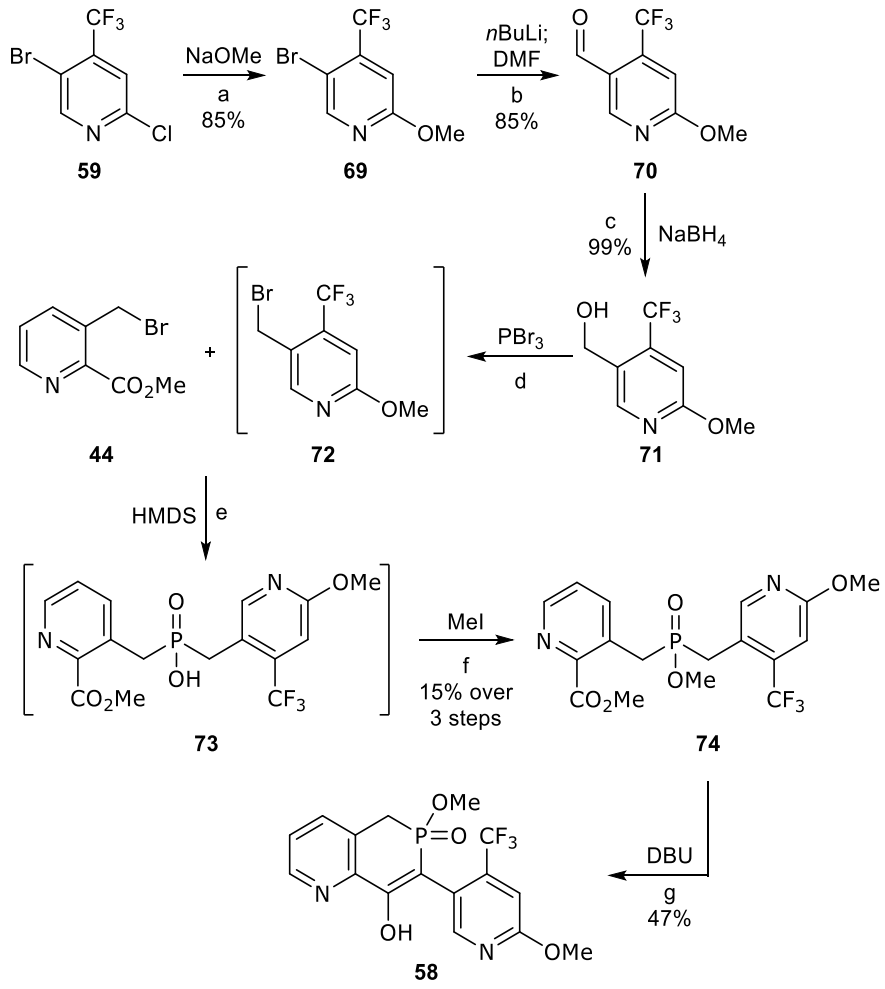


Scheme 27: *The final steps for the synthesis of phosphinate **57**. Reagents and conditions: a) PivCl (2.0 eq.), pyridine (4.0 eq.), toluene, 90 °C, 2 h. b)i) Cs_2CO_3 (3.0 eq.), DMF, 0 °C, 0.5 h ii) MeI (4.0 eq.), 0 °C – r.t., 16 h. c) LiOH•H_2O (3.0 eq.), THF/H_2O (1:1), r.t., 16 h.*

2.3.2. The Synthesis of Phosphinate **58**

The synthesis of phosphinate **58** was completed using the same strategy as the other analogues. Electrophile **72** was synthesised in four steps. Initially, a nucleophilic aromatic substitution reaction of commercially available pyridine **59**, with sodium methoxide, gave the desired 2-methoxypyridine **69** in 85% yield, Scheme 28. The formation of aldehyde **70** followed by the subsequent reduction, provided alcohol **71** in 84% yield over the two steps, Scheme 28. The bromination to form **72** was performed with PBr_3, and *via* an Appel reaction with PPh_3 and CBr_4. Under the Appel conditions at room temperature the alcohol **71** was unreactive. Nevertheless, the reaction with PBr_3 gave the desired electrophile **72**. Unfortunately, **72** was unstable and therefore was taken through to next step as the crude product, Scheme 28. The subsequent coupling of **72** and **44** with ammonium hypophosphite was performed with HMDS. Unlike with the previous syntheses of **19** and **57**, during

this synthesis, secondary phosphinic acid **73** was not isolated by reverse-phase column chromatography.



Scheme 28: *The synthesis of phosphinate **58**. Reagents and conditions: a) NaOMe (1.5 eq.), MeOH, r.t., 2 h. b)i) n-BuLi (1.0 eq., 1.6 M in hexanes), Et_2O/THF (2:1), – 78 °C, 0.75 h. ii) DMF (1.7 eq.), – 78 °C, 1.5 h. iii) sat.NH_4Cl. c) $NaBH_4$ (0.50 eq.), MeOH, 0 °C – r.t., 1 h. d) PBr_3 (1.5 eq.), CH_2Cl_2, r.t., 1.5 h. e)i) HMDS (1.0 eq.), 110 °C, 1.5 h. ii) 0°C, CH_2Cl_2, **72** (1.0 eq.), r.t., 17 h. iii) 0 °C, HMDS (1.0 eq.), 2 h. iv) 0 °C, **44** (1.0 eq.), CH_2Cl_2, r.t., 20 h. v) MeOH, r.t.. f) MeI (3.0 eq.), Cs_2CO_3 (3.0 eq.), MeCN, r.t., 80 °C, 1 h. g) DBU (2.5 eq.), MeCN, 60 °C, 16 h.*

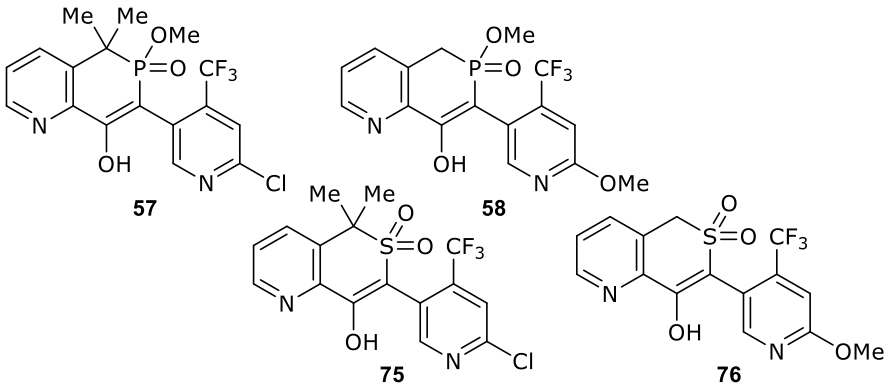
Instead methylation of the crude material was performed with methyl iodide, Scheme 28. The corresponding acyclic phosphinate **74** was isolated in 15% yield over the three steps. The final cyclisation was again achieved with DBU and gave

cyclic phosphinate **58** in 47%, Scheme 28. The final compound was isolated as a 1:1.2 mixture of atropisomers and the overall synthesis was completed in an overall yield of 5%.

2.3.3. Physical Chemistry and Biological Results for **57** and **58**

Both cyclic phosphinates **57** and **58**, and the corresponding sulfones **75** and **76**, were tested for herbicidal activity in a glasshouse assay and it was found that the phopshinates displayed moderate activity, Table 6.

Table 6: *The results from the glasshouse tests for herbicidal activity for **57**, **58**, **75** and **76**.*



Entry	Conc./ gha^{-1}	Plant Species (Post Emergence)					
		AMARE	ABUTH	SETFA	ECHCG	ZEAMX	IPOHE
57	500	70	70	80	80	50	30
	125	60	20	70	60	30	20
	31.25	50	20	40	40	10	10
75	500	90	90	90	90	90	80
	125	90	90	90	90	90	80
	31.25	90	80	90	90	90	80
58	500	60	30	70	60	20	20
	125	30	10	40	30	10	10
	31.25	40	20	30	20	0	10
76	500	90	90	90	90	90	40
	125	80	90	80	90	60	20
	31.25	70	80	70	60	60	50

The compounds were tested in three different concentrations (500, 125, 31.25 gha^{-1}) against six different plant species. The results are a measure of percentage phytotoxicity to the plant, where 100 is total damage to plant and 0 is no damage to plant. Although phosphinates **57** and **58** displayed moderate activity, their sulfone counterparts were far more potent, with a percentage phytotoxicity often over 80. The physical chemistry and *in-vitro* potency data were also obtained for **57** and **58**, Table 7. It demonstrated that the phosphinate analogues **57** and **58** had similar LogP values when compared to their sulfones counterparts, **75** and **76**. However, the main difference between the two sets of compounds was the acidity of the enol moiety. It was found that the alcohol in the sulfone compounds **75** and **76** were far more acidic with pKa values of 4.55 and 4.68, respectively. Whereas the phosphinates **57** and **58** had pKa values of 6.14 and 6.40, respectively. This suggests that a sulfone functional group is far more electron-withdrawing compared to a methylphosphinate moiety. The *in-vitro* potency for each compound was also tested. The value given is the half-life of the compound in hours, and a larger half-life corresponds to a compound displaying stronger binding to 4-HPPD.

Table 7: *The physical chemistry and in-vitro potency results for **57**, **58**, **75** and **76***

Entry	Phosphinate or Sulfone	Acidic pKa	LogP	HPPD $T_{1/2}$ / h
57	Phosphinate	6.14	1.77	18.43
75	Sulfone	4.55	1.62	44.78
58	Phosphinate	6.40	1.25	6.815
76	Sulfone	4.68	1.21	6.397

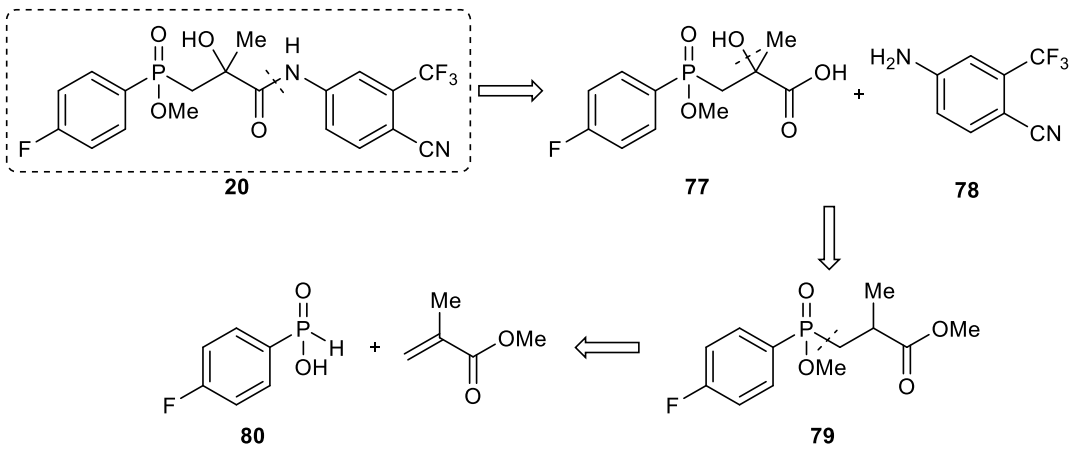
When comparing phosphinate **57** and sulfone **75**, it can be seen that sulfone **75** is far superior at binding to 4-HPPD, with an off-rate $T_{1/2}$ of 44.78 hours. However, when phosphinate **58** and sulfone **76** are compared, it is observed that the phosphinate has a slightly longer $T_{1/2}$ than its sulfone counterpart, Table 7. There was no doubt that sulfone **76** demonstrates greater herbicidal activity, Table 6.

Nevertheless, it was interesting to see that the only significant difference in the physical chemistry and *in-vitro* potency data, between **58** and **76**, was the acidity of the enol, Table 7. It is hypothesised that the increased herbicidal activity of **76** is due to an increased bioavailability in the plant, as a result of the lower pKa, likely due to higher phloem mobility. Although the sulfone analogues display more potent herbicidal activity, it was encouraging to see that the phosphinate did bind to the same target, which is a key attribute of a bioisostere.

2.4. A Phosphinate Analogue of Casodex®

2.4.1. Retrosynthetic Analysis

The next target for this investigation was a methylphosphinate analogue of Casodex®. Casodex® is a pharmaceutical compound approved for the treatment of prostate cancer.[7,12–16] Although the active compound of Casodex® is known to be the *R*-enantiomer, the drug is actually a racemic mixture of both enantiomers, therefore the synthesis of phosphinate **20** will be a racemic synthesis.[12,15]



Scheme 29: *The retrosynthesic analysis of Casodex® analogue **20**.*

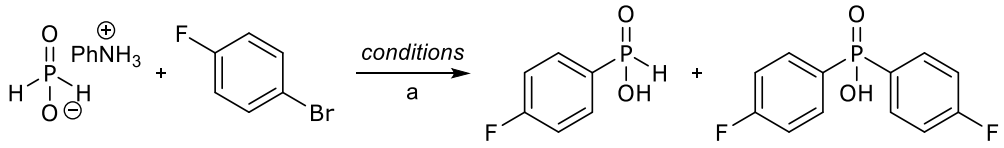
The retrosynthetic analysis began with a disconnection at the amide, Scheme 29. It was thought that this amide could constructed *via* any conventional amide coupling

reaction. It was envisaged that phosphinate **77** could be formed from the sequentially α-oxidation and hydrolysis of phosphinate **79**. In turn **79** was to be synthesised *via* a *P-C* bond forming reaction between 4-fluorophenylphosphinic acid **80** and methyl methacrylate, Scheme 29. It was thought that the silyl-phosphinate discussed in Part 1 Chapter 2 could be used for this reaction.

2.4.2. Forward Synthesis

In 2009, Stawinksi and co-workers reported a microwave-assisted palladium catalysed cross-coupling reaction for the synthesis of primary phosphinic acids.[44] It was reasoned that this method could be used to synthesise 4-fluorophenylphosphinic acid **80**.

Table 8: *The palladium-catalysed cross-coupling to synthesis phosphinic acid **80**.*



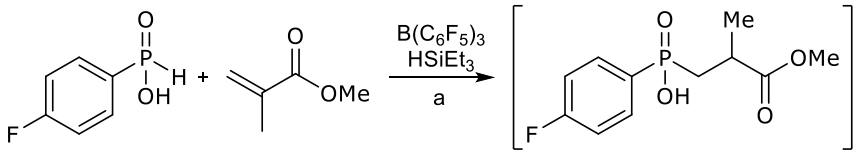
81 **80** **82**

Entry	Cat. Loading / mol%	**81** / eq.	μW or thermal	Temp. / °C	Time / min	**80**:**82**[b]	NMR yield[c] / %	Yield / %
1	5	1.0	μW	120	10	-	31	-
2	2	1.0	μW	120	10	-	73	-
3	2	1.0	μW	120	10	81:19	-	-
4	2	0.50	μW	120	10	96:4	-	57
5	2	0.50	thermal	reflux	10	-	50	-
6	2	0.50	thermal	reflux	30	-	80	-
7	2	0.50	thermal	reflux	60	-	91	-
8	2	0.50	thermal	reflux	60	100:0	-	67

*Reagents and conditions: a) anilinium hypophosphite (1.0 eq.), **81** (eq.), $Pd_2(dba)_3$•$CHCl_3$ (mol%), Xantphos (mol%), NEt_3 (2.5 eq.), THF, temp., time. b) by ^1H NMR spectroscopy. c) by ^{31}P decig NMR spectroscopy, 64 or 128 scans, 30 s delay, internal standard PPh_3O (0.05 mmol).*

Initially, the reaction was performed using microwave heating, as reported by Stawinski and co-workers.[44] We used 2 mol% catalyst loading and reaction monitoring by ^{31}P NMR spectroscopy suggested that **80** was forming relatively cleanly, Table 8 Entry 1. However, when the reaction was scaled-up and isolated significant quantities of the secondary phosphinic acid **82** were formed, Table 8 Entry 3. The problem was mostly solved by using 0.5 equivalents of the aryl halide **81**, and the desired primary phosphinic acid **80** was isolated in 57% yield, Table 8 Entry 4. On a large scale the use of a microwave was impractical therefore the reaction was adjusted for thermal heating. The same catalyst loading, solvent and base as the original procedure was used and after 1 hour at reflux the product **80** was formed in 91% by ^{31}P NMR spectroscopy, Table 8 Entry 5 - 7. The updated conditions were employed on a large scale synthesis of 4-fluorophenylphosphinic acid **80**, and the product was isolated in 67% yield, Table 8 Entry 8.

With phosphinic acid **80** in hand, the step next was the construction of the key *P-C* bond. This was attempted using the silyl-phosphonite chemistry discussed in Part 1 Chapter 2. The standard reaction conditions were employed (*see Part 1 Chapter 2*), although 4.0 equivalents of methyl methacrylate were required to consume all the phosphinic acid starting material, Scheme 30.

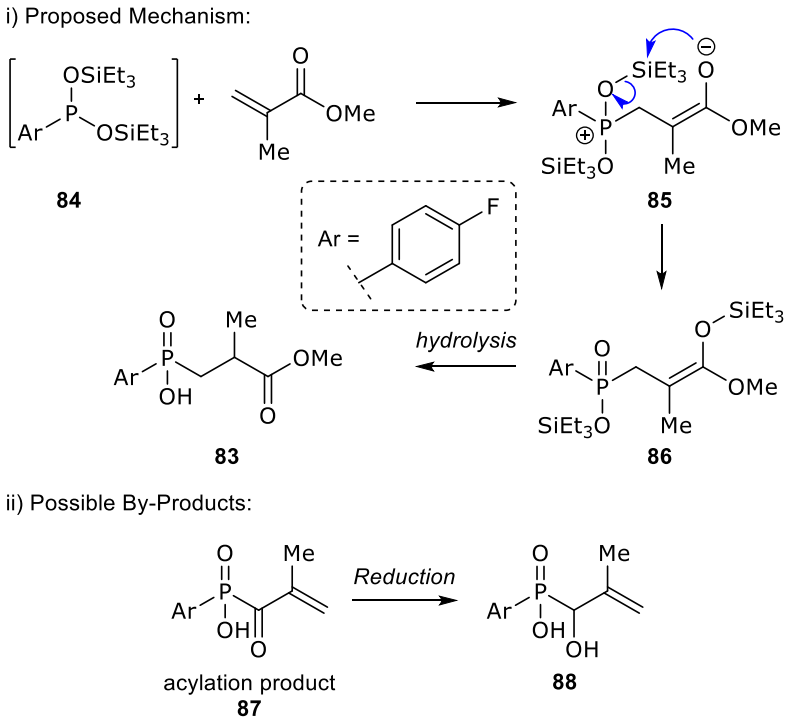


80 **83**

Scheme 30: The synthesis of phosphinic acid **83**. Reagents and conditions: *a) $B(C_6F_5)_3$ (3.5 mol%), $HSiEt_3$ (3.5 eq.), toluene, 100 °C, 16 h.*

Under these conditions other unknown phosphorus by-products were observed. The by-products were not isolated but some possible structures have been proposed, Scheme 31ii. The mechanism of the reaction is reasoned to proceed *via* the 1,4-

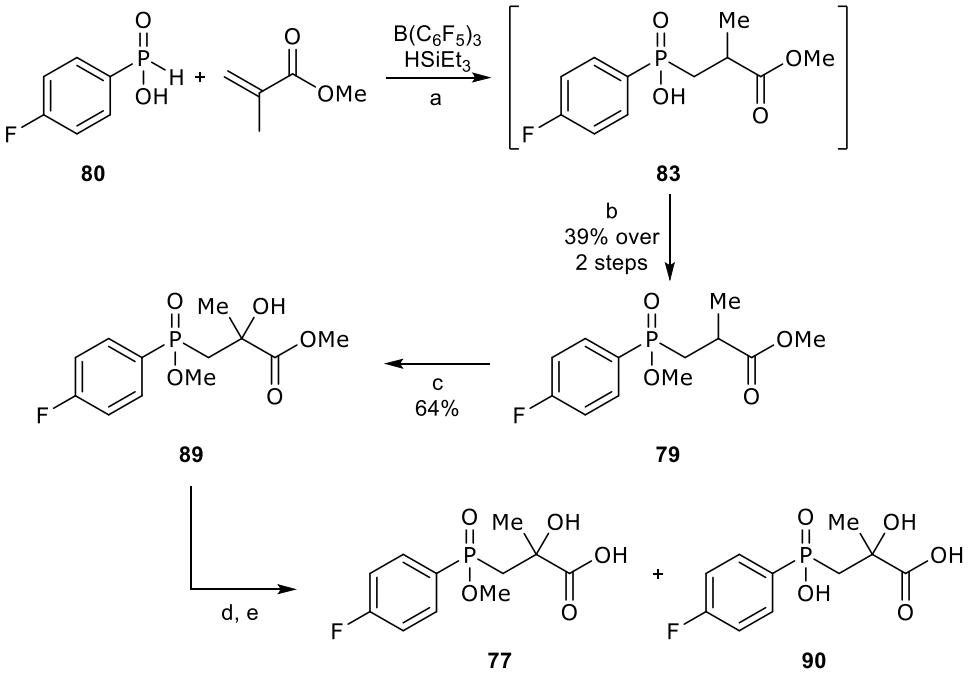
conjugate addition of silyl-phosphonite **84** with the acrylate, in the manner depicted in Scheme 31i. However, possible by-products could arise from the acylation reaction of the silyl-phosphinate with the ester moiety. The α-keto compound **87** would most likely then be reduced to give the α-hydroxy species **88**, Scheme 31ii.



Scheme 31: *i) The proposed mechanism for the 1,4-addition reaction. ii) Possible by-products during the reaction.*

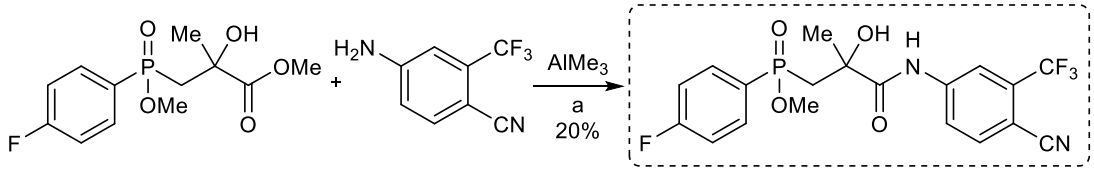
The desired secondary phosphinic acid **83** could not be isolated, instead the methylphosphinate **79** was obtained in 39% yield over two steps, following the methylation with (trimethylsilyl)diazomethane, Scheme 32. Deprotonation of **79** with KHMDS generated the corresponding enolate, which was then oxidised with molecular oxygen, in the presence of a $P(OEt)_3$ reductant. The corresponding α-hydroxy product **89** was synthesised in 64% yield, Scheme 32. Unfortunately, the subsequent hydrolysis of **89** to the corresponding carboxylic acid **77** was unsuccessful. When the hydrolysis was attempted, with either LiOH or $KOSiMe_3$, a mixture of **77** and **90** was isolated, Scheme 32. The amide coupling reaction was

attempted on this crude mixture but no product was observed. It was clear that an alternative strategy was needed.



Scheme 32: *The synthesis of methylphosphinate **89** and the attempted hydrolysis to the corresponding carboxylic acid **77**. Reagents and conditions: a) $B(C_6F_5)_3$ (3.5 mol%), $HSiEt_3$ (3.5 eq.), toluene, 100 °C, 16 h. b) (trimethylsilyl)diazomethane (4.0 eq.), toluene/MeOH (4:1), 0 °C – r.t., 0.5 h. c)i) KHMDS (1.1 eq., 1.0 M solution in THF), THF, –78 °C, 0.75 h ii) $P(OEt)_3$ (2.0 eq.) iii) O_2 (balloon) iv) HCl (2.0 M aqueous solution), –78 °C – r.t.. d) $LiOH•H_2O$ (1.1 – 3.0 eq.), THF/H_2O (1:1), r.t., 3 – 5 h. e) $KOSiMe_3$ (1.0 – 2.0 eq.), THF, r.t., 16 – 18 h.*

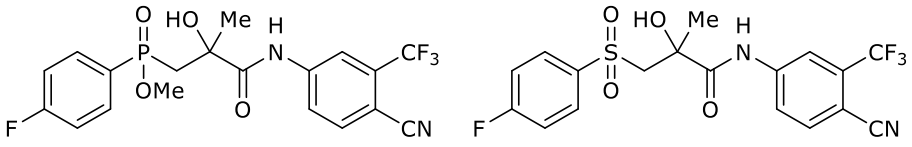
It was envisaged that the direct amidation reaction between aniline **78** and ethyl ester **89**, could be achieved using $AlMe_3$. The successful coupling of **78** and **89** required 3.5 equivalents of $AlMe_3$ but even with excess $AlMe_3$ there was still starting material remaining. However, complete degradation of the reaction mixture was observed if increased quantities of $AlMe_3$ were employed. Nevertheless, using this method the phosphinate analogue of Casodex® **20** was isolated in 20% yield as a 2:1 mixture of diastereomers, Scheme 33.



89 **78** **20**

Scheme 33: *The final amidation step to synthesise the **20** Reagents and conditions: a) **89** (1.0 eq.), **78** (1.0 eq.), $AlMe_3$ (3.5 eq., 2.0 M in hexanes), toluene, 0 °C – r.t., 16 h.*

In summary, the novel phosphinate analogue of Casodex® **20** was synthesised in an overall yield of 3%. Although some further optimisation of this route is required, enough material was obtained to test the activity of **20** in prostate cancer cell lines. Unfortunately, this has not yet been performed but is a priority for the future. Only the lipophilicity of **20** has been tested, and it was encouraging to see that the LogP value for **20** was similar to the literature values for Casodex®, Figure 11.[45,46]



20
3% over 5 steps
LogP: 2.60

Casodex® - **3**
LogP: 2.54 - 2.92

Figure 11: *The LogP values for Casodex® and **20**.*

2.5. Conclusion and Future Work

In conclusion, during the investigation into whether methylphosphinates can be bioisosteres for the sulfone group, five novel phosphinate analogues of known sulfones have been synthesised, while avoiding the use of PCl_3 or other halophosphines, Figure 12. From the physical data that was gathered of these analogues it was encouraging to see that the LogP values were similar to the sulfone compounds. However, the evidence has suggested that a sulfone is a far superior electron-withdrawing group compared to the corresponding methylphosphinates. This can be seen when comparing the pKa values of the sulfone and phosphinate 4-HPPD inhibitors in Section 2.2. This difference has hindered the biology activity of the tested phosphinates.

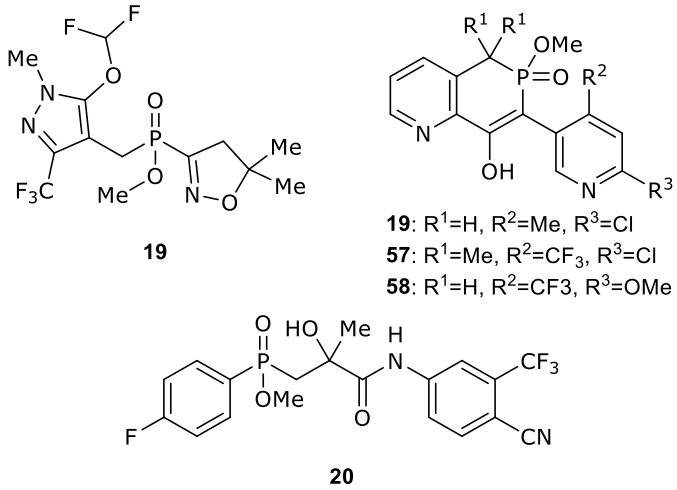


Figure 12: *The novel phosphinate analogues which have been synthesised.*

The analogue of Cadodex® **76** has not been tested in prostate cancer cell lines but this is a priority, and if it is shown to be active then an optimised route will need to be established. In the future, to further investigate whether phosphinates can be bioisosteres for the sulfone functional group, more analogues will need to be synthesised and tested.

Chapter 3 – Experimental

3.1. General Experimental

Commercially available reagents were used throughout without further purification unless otherwise stated. THF, Et_2O and toluene were obtained from a solvent tower where degassed solvent was passed through two columns of activated alumina and a 7 micron filter under a 4 bar pressure, then stored over a sodium wire. CH_2Cl_2 was either; stirred over calcium hydride, distilled and stored over 4 Å molecular sieves, or obtained from a solvent tower where degassed solvent was passed through two columns of activated alumina and a 7 micron filter under a 4 bar pressure, and stored over 4 Å molecular sieves. Water refers to deionised water and brine refers to a saturated solution of sodium chloride. Ether represents diethyl ether and light petroleum refers to the fraction with boiling range 40-60 °C.

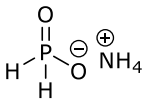
Analytical thin layer chromatography (TLC) was carried out on Merck TLC silica gel 60 F_{254} pre-coated aluminium sheets with fluorescent indicator, and visualised under UV light at 254 nm and/or stained using potassium permanganate. Column chromatography was carried out using Sigma Aldrich or Fluorochem silica gel 60 Å, 40-63 mesh with the eluent specified. Flash column chromatography was performed on Biotage Isolera apparatus with pre-packed silica gel columns. Microwave reactions were performed using a Biostage Initator.

Melting points were measured using Stuart SMP3 melting point apparatus or a GallenHamp melting point apparatus. High resolution mass spectra were recorded on a Bruker MicroTOF mass spectrometer using Electrospray Spray Ionisation (ESI) or Jeol AccuTOF GCX with Electron Ionisation (GC/EI-TOF). HRMS data were quoted to four decimal places (0.1 mDa). Fourier Transform Infrared Spectrometry (FTIR) was carried out using a Bruker Tensor 27 using an Attenuated Total Reflection (ATR) attachment and peaks are reported in terms of frequency of

absorption (cm-1). NMR spectra were recorded at the frequencies stated using Bruker DPX300, DPX400, AV400, AV(III)400, AV(III)400HD or AV(III)500. Chemical shifts are quoted in parts per million (ppm) referenced against the residual protonated solvent as an internal standard. Residual solvent signals are as follows: $CDCl_3$ is referenced at δ 7.26 and 77.16 for 1H and 13C NMR respectively, DMSO-d6 is referenced at δ 2.50 and 39.52 for 1H and 13C NMR respectively, CD_3OD is referenced at δ 3.31 and 49.00 for 1H and 13C NMR respectively and D_2O is reference to δ 4.79 in the ^1H NMR. Coupling constants *J* are quoted in Hertz (Hz).

3.2. Experimental Procedures

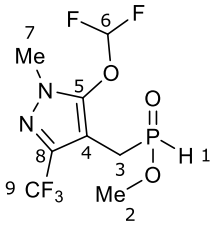
ammonium hypophosphite



To a stirred solution of hypophosphorus acid (22.9 mL of a 50% wt. H_2O solution, 0.500 mol) at 0 °C was added ammonium hydroxide (54.7 mL of a 25% wt. H_2O solution, 0.500 mol) dropwise. The reaction mixture was allowed to warm to r.t. and stirred for 0.5 h. The reaction mixture was concentrated *in vacuo* and then recrystalised from MeOH, filtered and washed with ice cold MeOH. The solid was dried in a vacuum desiccator over $CaCl_2$ at r.t. for 16h and the *title compound* was isolated as white crystals (29.3 g, 71%).

^{1}H NMR (400 MHz, deuterium oxide) δ 7.03 (d, J_{HP} = 518.3 Hz, 2H); ^{31}P NMR (162 MHz, deuterium oxide) δ 7.00 (t, J_{PH} = 518.3 Hz).

methyl ((5-(difluoromethoxy)-1-methyl-3-(trifluromethyl)-1H-pyrazol-4-yl)methyl)phosphinate (21)



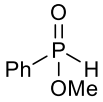
A stirred solution of ammonium hypophosphite (4.98 g, 60.0 mmol) and HMDS (13.2 mL, 63.0 mmol) was heated to 110 °C for 2 h under a constant flow of argon conditions. The reaction was cooled to 0 °C, diluted with CH_2Cl_2 (50 mL). **24** (3.71 g, 12.0 mmol) was added in a solution of CH_2Cl_2 (10 mL). The reaction was allowed to warm to r.t. and stirred for 16 h. The reaction was quenched with MeOH and the solution was concentrated *in* vacuo then partitioned between Et_2O and NaOH (1.0 M aqueous solution). The biphasic mixture was separated and extracted with NaOH

(1.0 M aqueous solution, × 2). The aqueous extracts were acidified to pH 1 with HCl (3.0 M aqueous solution) then re-extracted with EtOAc (× 3). The combined organic extracts were washed with brine (x 1), dried over $MgSO_4$, filtered, concentrated *in vacuo* and azeotroped with cyclohexane. The *title compound* was isolated as a colourless crystalline solid (2.28 g). *Taken into the next step crude with no further purification.*

To a stirred solution of **23** (2.01 mmol, 592 mg) in toluene/ MeOH (4:1, 10 mL) was added TMS-diazomethane (4.0 mL of a 2.0 M in hexanes, 8.0 mmol) until the yellow colouration persisted. The reaction was stirred at r.t. for 25 min. The reaction was quenched with acetic acid (conc.) and stirred for 30 min. The MeOH was removed *in vacuo* then diluted with EtOAc and washed with H_2O (x 3), brine (x 3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (40% EtOAc in CH_2Cl_2) and the *title compound* was isolated as a colourless oil (516 mg, 54% over two steps).

R_f: 0.31 (40% EtOAc in CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.05 (d, J_{HP} = 559.4 Hz, 1H, H - 1), 7.01 (dd, J_{HF} = 73.2, J_{HF} = 71.3 Hz, 1H, H - 6), 3.82 (s, 3H, H - 7), 3.80 (d, J_{HP} = 11.9 Hz, 3H, H - 2), 3.07 (d, J_{HP} = 16.8 Hz, 2H, H - 3); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 144.4 (Cq, C - 5), 138.9 (Cq, qd, J_{CF} = 37.4, J_{CP} = 3.6 Hz, C - 8), 121.0 (Cq, q, J_{CF} = 269.5 Hz, C - 9), 117.0 (CH, t, J_{CF} = 269.7 Hz, C-6), 97.2 (Cq, d, J_{CP} = 6.8 Hz, C - 4), 53.3 (CH_3, d, J_{CP} = 7.2 Hz, C - 2), 36.1 (CH_3, C - 7) , 23.6 (CH_2, d, J_{CP} = 92.5 Hz, C - 3); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -61.4 (d, J_{FP} = 2.2 Hz), -80.4 (dd, J_{FF} = 161.0, J_{FH} = 72.3 Hz), -81.6 (dd, J_{FF} = 161.0, J_{FH} = 72.3 Hz); ^{31}P NMR (162 MHz, chloroform-*d*) δ 33.6 (d, J_{PH} = 559.8 Hz)*; HRMS (ESI$^+$) $C_8H_{11}F_5N_2O_3PH^+$ $[M+H]^+$ calcd. 309.0422, found 309.0427; IR (ATR) ν_{max} 2922, 2351, 2118, 1583, 1491, 1388, 1286, 1171, 1125, 1063, 985. *Only J^1 coupling reported.

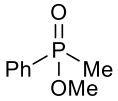
methyl phenylphosphinate (33)[47]



To a stirred solution of phenylphosphinic acid (710 mg, 5.00 mmol) in toluene/MeOH (4:1, 25 mL) was added trimethylsilyldiazomethane (10 mL of a 2.0 M solution in hexanes, 20 mmol) over 45 min at r.t. until the yellow colouration persisted. The reaction was stirred at r.t for 1 h then the reaction was then quenched with excess acetic acid and stirred for 1 h. The solvent was removed *in vacuo* and partitioned between EtOAc and brine. The biphasic mixture was separated and further extracted with EtOAc (× 2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (100% EtOAc) and *the title compound* was isolated as a colourless oil (730 mg, 94%).

R_f: 0.19 (100% EtOAc); ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.87 – 7.67 (m, 2H), 7.68 – 7.57 (m, 1H), 7.56 (d, J_{HP} = 565.6 Hz, 1H), 7.57 – 7.44 (m, 2H), 3.79 (dd, J_{HP} = 12.0, J_{HH} = 0.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 133.3 (CH, d, J_{CP} = 3.0 Hz), 131.1 (CH, d, J_{CP} = 12.2 Hz), 130.2 (Cq), 128.9 (CH, d, J_{CP} = 13.8 Hz), 52.3 (CH_3, d, J_{CP} = 6.6 Hz); ^{31}P NMR (121 MHz, chloroform-*d*) δ 27.1 (d, J_{PH} = 564.3 Hz)*; HRMS (ESI$^+$) $C_7H_9O_2PNa^+$ $[M+Na]^+$ calcd. 179.0232, found 179.0234. *Only J^1 coupling reported.

methyl methyl(phenyl)phosphinate (34)[48]

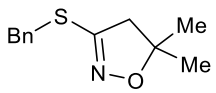


To stirred solution of NaH (58 mg, 2.4 mmol, neat) in THF (25 ml) at r.t. was added **33** (312 mg, 2.00 mmol) in THF (2.5 mL) and then the mixture was stirred for 1 h. MeI (0.37 mL, 6.0 mmol) was added dropwise then the reaction mixture was stirred

for 16 h. The reaction was quenched with H_2O and the THF was removed *in vacuo*. The residue was partitioned between H_2O and CH_2Cl_2 and extracted with CH_2Cl_2 (× 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil. The crude material was purified by silica gel chromatography (5% MeOH in CH_2Cl_2) and the *title compound* was isolated as a light yellow oil (230 mg, 68%).

R_f: 0.17 (5% MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.83 – 7.75 (m, 2H), 7.60 – 7.54 (m, 1H), 7.53 – 7.46 (m, 2H), 3.61 (d, J_{HP} = 11.3 Hz, 3H), 1.67 (d, J_{HP} = 14.6 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 132.5 (CH, d, J_{CP} = 2.9 Hz), 131.5 (CH, d, J_{CP} = 10.0 Hz), 131.2 (Cq, d, J_{CP} = 126.5 Hz), 128.8 (CH, d, J_{CP} = 12.5 Hz), 51.2 (CH_3, d, J_{CP} = 6.4 Hz), 15.7 (CH_3, d, J_{CP} = 103.1 Hz); ^{31}P NMR (162 MHz, chloroform-*d*) δ 44.0 (m); HRMS (ESI$^+$) $C_8H_{11}NaO_2P^+$ $[M\text{-}H]^-$ calcd. 193.0389, found 193.0393.

3-(benzylthio)-5,5-dimethyl-4,5-dihydroisoxazole (37)[49]

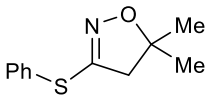


To a stirred solution of **22** (125 mg, 0.937 mmol) and K_2CO_3 (842 mg, 6.09 mmol) in DMF (3.5 mL) at r.t. was added benzyl mercaptan (0.11 mL, 0.94 mmol). The reaction was stirred at r.t. for 5 h and was filtered, diluted with H_2O and extracted with EtOAc (× 3). The combined organic extracts were washed with H_2O (× 3) and brine (× 2) then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (5 – 10% EtOAc in petrol) and the *title compound* was isolated as a white solid (123 mg, 59%).

R_f: 0.30 (5% EtOAc in petrol); m.p.: 52 – 54 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41 – 7.26 (m, 5H), 4.27 (s, 2H), 2.78 (s, 2H), 1.41 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 155.0 (Cq), 136.7 (Cq), 129.2 (CH), 128.8 (CH), 127.7 (CH), 84.7

(Cq), 50.5 (CH_2) , 35.6 (CH_2) , 27.0 (CH_3); HRMS (ESI^+) $C_{12}H_{15}ONSNa^+$ $[M+Na]^+$ calcd. 244.0767, found 244.0768.

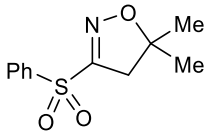
5,5,dimethyl-3-(phenylthio)-4,5-dihydroisoxazole (41) [50]



A stirred solution **22** (1.07 g, 8.00 mmol), K_2CO_3 (7.19 g, 52.0 mmol) in DMF (30 mL) was degassed, then thiophenol (0.82 mL, 8.0 mmol) was added at r.t. and stirred for 3 h. Thiophenol (0.98 mL, 12 mmol) was added and the reaction mixture was stirred at r.t. for 20 h. Thiophenol (3.28 mL, 32.0 mmol) was added and the reaction stirred at r.t. for 3 days. The reaction was diluted with H_2O and extracted with EtOAc (× 3). The combined organic extracts were washed with H_2O (× 2), brine (× 2), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. The crude material was purified by silica gel column chromatography (1 – 10% EtOAc in petrol) and the *title compound* was isolated as a light yellow oil (1.03 g, 62%).

R_f: 0.24 (10% EtOAc in petrol); ^1H NMR (400 MHz, chloroform-*d*) δ 7.62 – 7.48 (m, 2H), 7.42 – 7.32 (m, 3H), 2.71 (s, 2H), 1.39 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*) δ 155.5 (Cq), 133.7 (CH), 129.5 (CH), 129.5 (Cq), 85.0 (Cq), 50.2 (CH_2), 27.0 (CH_3); HRMS (ESI^+) $C_{11}H_{13}ONSNa^+$ $[M+Na]^+$ calcd. 230.0610, found 230.0612.

5,5-dimethyl-3-(phenylsulfonyl)-4,5-dihydroisoxazole (42)[50]

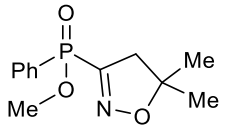


To a stirred solution of *m*-CPBA (2.12 g, 12.3 mmol, 70% purity) in CH_2Cl_2 (40 mL) was added **41** (1.02 g, 4.92 mmol) as a solution in CH_2Cl_2 (9.0 mL) at r.t. The reaction was stirred at r.t. for 24 h. The reaction was diluted with H_2O and EtOAc.

The biphasic mixture was separated and further extracted with EtOAc (× 2). The combined organic extracts were washed with aq. $Na_2S_2O_5$, sat. $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo* and gave *the title compound* as a colourless solid (1.12 g, 95%).

m.p.: 51 – 52 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.05 – 7.95 (m, 2H), 7.75 – 7.69 (m, 1H), 7.64 – 7.58 (m, 2H), 3.07 (s, 2H), 1.44 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 159.7 (Cq), 137.6 (Cq), 134.8 (CH), 129.5 (CH), 129.0 (CH), 90.2 (Cq), 44.1 (CH_2) , 27.1 (CH_3); HRMS (ESI$^+$) $C_{11}H_{13}O_3NSNa^+$ $[M+Na]^+$ calcd. 262.0508 found 262.0507.

methyl (5,5-dimethyl-4,5-dihydroisoxazol-3-yl)(phenyl)phosphinate (35)

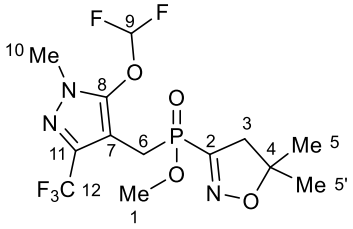


To a stirred solution of NaH (25 mg, 1.0 mmol, neat) in THF (3.0 mL) was added **42** (147 mg, 0.941 mmol) as a solution in THF (2.0 mL) at r.t. then stirred at r.t. for 1 h. The reaction mixture was cooled to – 78 °C then **33** (150 mg, 0.627 mmol) as a solution in THF (4.0 mL) was added dropwise. The reaction mixture was stirred at – 78 °C for 1 h. The reaction was quenched with sat. NH_4Cl (10 mL) and diluted with EtOAc. The biphasic mixture was separated and further extracted with EtOAc (× 2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (100% EtOAc) to give *the title compound* as a colourless oil (129 mg, 81%).

R_f: 0.29 (100% EtOAc); ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.91 – 7.83 (m, 2H), 7.65 – 7.58 (m, 1H), 7.55 – 7.48 (m, 2H), 3.85 (d, J_{HP} = 11.5 Hz, 3H), 3.01 (dd, J_{HH} = 17.2, J_{HP} = 1.4 Hz, 1H), 2.85 (dd, J_{HH} = 17.2, J_{HP} = 1.4 Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 153.8 (Cq, d, J_{CP} = 154.0 Hz), 133.4 (CH, d, J_{CP} = 2.9 Hz), 132.2 (CH, d, J_{CP} = 10.6 Hz), 128.9 (CH, d, J_{CP} = 13.9 Hz),

128.1 (Cq, d, J_{CP} = 145.6 Hz) , 86.4 (Cq, d, J_{CP} = 5.9 Hz), 52.6 (CH_3, d, J_{CP} = 6.0 Hz), 48.0 (CH_2, d, J_{CP} = 14.8 Hz,), 27.1 (CH_3), 27.1 (CH_3); ^{31}P NMR (162 MHz, chloroform-*d*) δ 24.0 (m); HRMS (ESI$^+$) $C_{12}H_{16}O_3NPNa^+$ $[M+Na]^+$ calcd. 276.0760, found 276.0760; IR (ATR) ν_{max} 3058, 2974, 2850, 1233, 1022.

Methyl ((5-(difluromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)methyl)(5,5-dimethyl-4,5-dihydroisoxazol-3-yl)phosphinate (18)

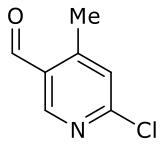


To a stirred solution of **21** (276 mg, 0.895 mmol) and **42** (321 mg, 1.34 mmol) in THF (1.8 mL) at – 78 °C was added NaH (24 mg, 0.99 mmol, neat) portion wise. The reaction mixture was warmed to – 40 °C and stirred for 3 h. The reaction mixture was quenched with H_2O, warmed to r.t., diluted with brine and extracted EtOAc (x 3). The combined organic extracts were dried of $MgSO_4$, filtered and concentrated *in vacuo* to give a crude residue. The crude material was purified by silica gel column chromatography (1 – 3% MeOH in CH_2Cl_2) and the *title compound* was isolated as a pale yellow gum (239 mg, 67%).

R_f: 0.31 (3% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.08 (dd, J_{HF} = 74.2, J_{HF} = 71.1 Hz, 1H, H - 9), 3.84 (s, 3H, H - 10), 3.75 (d, J_{HP} = 11.3 Hz, 3H, H-1), 3.42 – 3.23 (m, 2H, H - 6), 2.93 (d, J_{HP} = 1.2 Hz, 2H, H - 3), 1.45 (s, 6H, H - 5); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 152.7 (Cq, d, J_{CP} = 143.8 Hz, C - 2), 144.6 (Cq, C - 8), 139.2 (Cq, qd, J_{CF} = 37.4, J_{CP} = 3.9 Hz, C - 11), 121.1 (Cq, q, J_{CF} = 269.6 Hz, C - 12), 117.2 (CH, ddd, J_{CF} = 269.5, J_{CF} = 266.3, J_{CP} = 3.2 Hz, C- 9), 97.2 (Cq, d, J_{CP} = 9.7 Hz, C - 7), 86.9 (Cq, d, J_{CP} = 5.7 Hz, C - 4), 53.0 (CH_3, d, J_{CP} = 7.8 Hz, C - 1), 47.9 (CH_2, d, J_{CP} = 13.6 Hz, C - 3), 36.2 (CH_3, C – 10), 27.3 (CH_3, C - 5/5'), 27.1 (C - 5/5'), 23.3 (CH_2, d, J = 104.2 Hz, C - 6); ^{19}F NMR (376 MHz,

Chloroform-*d*) δ -61.4, -80.5 (dd, J_{FF} = 161.2, J_{FF} = 74.2 Hz), -81.9 (dd, J_{FF} = 161.2, J_{FH} = 71.1 Hz); ^{31}P NMR (162 MHz, chloroform-*d*) δ 30.0 (m); HRMS (ESI$^+$) $C_{13}H_{17}F_5N_3NaO_4P$+ $[M+Na]^+$ calcd. 428.0769, found 428.0768; IR (ATR) υ_{max} 2976, 2962, 2926, 2853, 2351, 2358, 2299, 1427, 1287, 1172, 1062, 1035, 899 cm^{-1}.

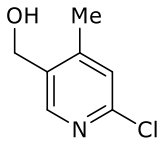
6-chloro-4-methylnicotinaldehyde (49)



To a stirred solution of 5-bromo-2-chloro-4-methylpyridine **48** (4.97 g, 24.1 mmol) in Et_2O (154 mL) was added *n*-BuLi (12.1 mL of a 2.0 M solution in hexanes, 24.1 mmol) at –78 °C at a rate of 60 mL/h. The reaction was held at –78 °C for 45 min then DMF (261 mL, 33.7 mmol) was added at – 78 °C at a rate of 40 mL/h. The reaction was held at –78 °C for 1.5 h then was quenched with sat. NH_4Cl. The Et_2O and hexanes were removed *in vacuo* and the remaining solution was extracted with CH_2Cl_2 (x 3). The combined organic extracts were then washed with brine (x 2), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a dark orange oil. The crude material was purified by silica gel column chromatography (2 – 10% EtOAc in CH_2Cl_2) and the *title compound* was isolated as a pale yellow crystalline solid (2.66 g, 71%).

R_f: 0.41 (2% EtOAc in CH_2Cl_2); m.p.: 70 – 72 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.23 (s, 1H), 8.71 (s, 1H), 7.27 (s, 1H), 2.67 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 190.6 (CH), 156.0 (Cq), 154.7 (CH), 152.2 (Cq), 129.0 (Cq), 127.0 (CH), 19.7 (CH_3); HRMS (ESI$^+$) $C_7H_7{}^{35}ClNO^+$ $[M+H]^+$ calcd. 156.0211, found 156.0213; IR (ATR) υ_{max} 3051, 2876, 2752, 1693, 1093, cm^{-1}.

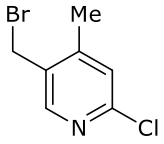
(6-chloro-4-methylpyrin-3-yl)methanol (50)



To a stirred solution of **49** (2.66 g, 17.1 mmol) in methanol (68 mL) was added $NaBH_4$ (323 mg, 8.55 mmol) at 0 °C. The reaction was warmed to r.t. and stirred for 1 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with brine (x 1), dried over $MgSO_4$, filtered and concentrated *in vacuo* and the *title compound* was isolated as a yellow oil (2.48 g, 92%).

^1H NMR (400 MHz, chloroform-*d*) δ 8.26 (s, 1H), 7.15 (s, 1H), 4.71 (d, J_{HH} = 4.0 Hz, 2H), 2.37 (s, 3H), 2.01 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*) δ 151.1 (Cq), 149.5 (Cq), 148.6 CH), 133.5 (Cq), 125.5 (CH), 60.7 (CH_2), 18.4 (CH_3); HRMS (ESI^+) $C_7H_9{}^{35}ClNO^+$ $[M+H]^+$ calcd. 158.0367, found 158.0372; IR (ATR) υ_{max} 3315, 2924, 2855, 1091.

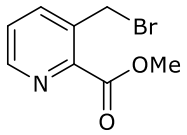
5-(bromomethyl)-2-chloro-4-methylpyridine (47)[26]



To a stirred solution of (6-chloro-4-methylpyrin-3-yl)methanol **50** (2.48 g, 15.7 mmol) in CH_2Cl_2 (50 mL) was added PBr_3 (7.22 mL, 23.6 mmol) at 0 °C. The reaction was warmed to r.t. and stirred for 2 h. The reaction was quenched with sat. $NaHCO_3$ at 0 °C then washed with sat. $NaHCO_3$ (x 2), brine (x 2). The aqueous washed were extracted with CH_2Cl_2 (x 2). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was then dried in a vacuum desiccator over CaCl for 16 h and the *title* compound was isolated as a light yellow solid (3.16 g, 91%).

m.p.: 68 – 70 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.27 (s, 1H), 7.18 (s, 1H), 4.45 (s, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 151.9 (Cq), 150.1 (CH), 149.8 (Cq), 131.4 (Cq), 125.9 (CH), 27.3 (CH_2), 18.5 (CH_3); HRMS (ESI^+) $C_7H_8{}^{79}Br^{35}ClN^+$ $[M+H]^+$ calcd. 219.9523, found 219.9519.

methyl 3-(bromomethyl)picolinate) (44)[51]



Method 1:

A stirred solution of 3-methylpicolinate **51** (1.35 mL, 10.0 mmol) in benzene (20 mL) was sparged with argon then NBS (890 mg, 5.00 mmol) and AIBN (82 mg, 0.50 mmol) were added sequentially at r.t. The reaction was heated to 85 °C and stirred for 2 h. The reaction mixture was cooled to r.t. then a second batch of NBS (890 mg, 5.00 mmol) and AIBN (82 mg, 0.50 mmol) were added. The reaction mixture was heated to 85 °C and stirred for 2 h then concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (5 – 10% EtOAc in CH_2Cl_2) to give yellow solid. The purified material was dried in a vacuum desiccator over CaCl at r.t. and the *title compound* was isolated as a pale yellow solid (1.38 g, 60%).

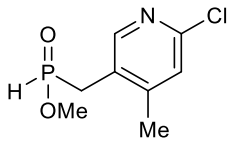
Method 2:

To a stirred solution of methyl picolinate **51** (8.40 g, 55.6 mmol) in trifluorotoluene (110 mL) was sparged with argon then at r.t. NBS (4.95 g, 27.8 mmol) and AIBN (228 mg, 1.39 mmol) were added. The reaction mixture was heated to 85 °C for 1 h. Another two batches of NBS (4.95 g, 27.8 mmol) and AIBN (228 mg, 1.39 mmol) were added each followed by 1 h heating at 85 °C. The reaction mixture was cooled to r.t. and quenched with sat. $Na_2S_2O_3$. The solution was diluted with H_2O and brine

then extracted with EtOAc (x 2) and CH_2Cl_2 (x 1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil. The crude material was purified by silica gel flash chromatography (0 – 10% EtOAc in CH_2Cl_2) and the *title compound* was isolated as a give pale yellow crystalline solid (5.72 g, 40%).

R_f 0.28 (5% EtOAc in CH_2Cl_2); m.p.: 69 - 71 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 (dd, J_{HH} = 4.6, J_{HH} = 1.6 Hz, 1H), 7.89 (dd, J_{HH} = 7.9, J_{HH} = 1.6 Hz, 1H), 7.47 (dd, J_{HH} = 7.9, J_{HH} = 4.6 Hz, 1H), 4.94 (s, 2H), 4.03 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.8 (Cq), 149.1 (CH), 146.3 (Cq), 140.0 (CH), 135.7 (Cq), 126.7 (CH), 53.2 (CH_3), 29.3 (CH_2); HRMS (ESI$^+$) $C_8H_8N_2O_2{}^{79}BrNa^+$ $[M+Na]^+$ calcd. 251.9631, found 251.9638.

Methyl ((6-chloro-4-methylpyridin-3-yl)methyl)phosphinate (45)



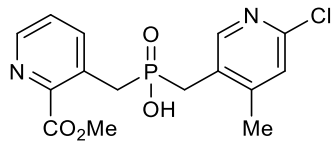
A stirred solution of HMDS (1.36 mL, 6.51 mmol) and ammonium hypophosphite (515 mg, 6.20 mmol) was heated to 110 °C for 2 h under a constant flow of argon. The reaction mixture was cooled to 0 °C and was diluted with CH_2Cl_2 (3.0 mL), then **47** (1.00 g, 6.20 mmol) in CH_2Cl_2 (2.0 mL). The reaction mixture was warmed to r.t. and stirred for 18 h then was quenched with excess MeOH. The solution was concentrated *in vacuo* to give a yellow residue which was diluted with the minimal amount of CH_2Cl_2 and was filtered. The filtrate was concentrated *in vacuo* to give a crude yellow gum (1.27 g).

The crude material was dissolved in toluene/MeOH (4:1, 30 mL) and TMS-diazomethane (10 mL of a 2.0 M solution in hexanes, 20 mmol) was added dropwise. The reaction was quenched with AcOH (conc.) and stirred for a further 15 mins, then the MeOH and hexanes were removed. The remaining solution was

neutralised to pH 7 with sat. $NaHCO_3$ and extracted with EtOAc (x 3). The organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. The crude material was purified by silica gel column chromatography (0 – 10% MeOH in EtOAc) and the *title compound* was isolated as a colourless oil (390 mg, 25% over the two steps).

R_f: 0.16 (5% MeOH in EtOAc); ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14 (d, J_{HP} = 2.9 Hz, 1H), 7.19 (s, 1H), 7.08 (dt, J_{HP} = 548.3, J_{HH} = 1.5 Hz, 1H), 3.76 (d, J_{HP} = 11.8 Hz, 3H), 3.19 (dd, J_{HP} = 17.9, J_{HH} = 1.5 Hz, 2H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 150.8 (Cq, d, J_{CP} = 4.4 Hz), 150.5 (CH, d, J_{CP} = 6.0 Hz), 149.8 (Cq, d, J_{CP} = 5.3 Hz), 125.8 (CH, d, J_{CP} = 3.5 Hz), 124.3 (Cq), 53.5 (CH_3, d, J_{CP} = 6.8 Hz), 31.2 (CH_2, d, J_{CP} = 89.3 Hz), 19.8 (CH_3); ^{31}P NMR (162 MHz, chloroform-*d*) δ 35.1 (d, J_{PH} = 548.5 Hz)*; HRMS (ESI$^-$) $C_8H_{12}{}^{35}ClNO_2P^+$ $[M+H]^+$ calcd. 220.0289, found 220.0305; IR (ATR) ν_{max} 2950, 2847, 1586, 1470, 1348, 1226, 1037, 967. *Only J^1 coupling reported.

((6-chloro-4-methylpyridin-3-yl)methyl)((2-(methoxycarbonyl)pyridine-3-yl)methyl)phosphinic acid (55)

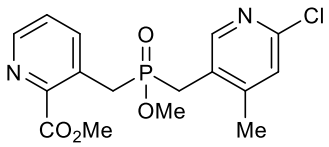


To a stirred solution of ammonium hypophosphite (1.20 g, 14.5 mmol) in HMDS (3.04 mL, 14.5 mmol) was heated to 110 °C for 2 h under a constant flow of N_2. The reaction mixture was cooled to 0 °C and diluted with CH_2Cl_2 (10.0 mL). **47** (3.20 g, 14.5 mmol) in CH_2Cl_2 (4.5 mL) was added then the reaction mixture was warmed to r.t. for 18 h. The reaction was cooled to 0 °C and HMDS (3.04 mL, 14.5 mmol) was added and the mixture was held at 0 °C for 2 h. **44** (3.88 g, 14.5 mmol) in CH_2Cl_2 (7.3 mL) was added and the reaction mixture was warmed to r.t. for 18 h. The mixture was cooled to 0 °C and quenched with MeOH. The solution was then

concentrated *in vacuo* to give a residue which was triturated with CH_2Cl_2 (x 3). The washings were concentrated *in vacuo* to give an orange gum. The crude material was purified by reverse-phase column chromatography (10 – 30% MeCN in H_2O with 0.1% formic acid) and the *title* compound was isolated as a white powder (2.08 g, 41%).

m.p.: 170 – 172 °C; ^{1}H NMR (500 MHz, methanol-d_4) δ 8.54 (apparent dt, J_{HH} = 4.8, J_{HH} =1.8 Hz, 1H), 8.15 (d, J_{HP} = 2.6 Hz, 1H), 7.96 (apparent dt, J_{HH} = 8.0, J_{HH} = 1.9 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.31 (s, 1H), 3.93 (s, 3H), 3.81 (d, J_{HP} = 16.6 Hz, 2H), 3.26 (d, J_{HP} = 15.3 Hz, 2H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, methanol-d_4) δ 167.5 (Cq), 152.7 (Cq, d, J_{CP} = 4.8 Hz), 151.4 (CH, d, J_{CP} = 5.0 Hz), 150.5 (Cq, d, J_{CP} = 3.7 Hz), 148.3 (Cq, d, J_{CP} = 5.7 Hz), 148.2 (CH, d, J_{CP} = 3.0 Hz), 142.8 (CH, d, J_{CP} = 4.6 Hz), 131.8 (Cq, d, J_{CP} = 9.2 Hz), 128.5 (Cq, d, J_{CP} = 9.3 Hz), 127.7 (CH, d, J_{CP} = 2.7 Hz), 126.6 (CH, d, J_{CP} = 2.7 Hz), 53.2 (CH_3), 34.7 (CH_2, d, J_{CP} = 86.0 Hz), 31.9 (CH_2, d, J_{CP} = 88.7 Hz), 19.7 (CH_3); ^{31}P{^{1}H} NMR (202 MHz, methanol-d_4) δ 41.5; HRMS (ESI$^-$) $C_{15}H_{15}{}^{35}ClN_2O_4P^-$ $[M-H]^-$ calcd. 353.0463, found 353.0468; IR (ATR) ν_{max} 2991, 2953, 2656, 2314, 2121, 1719, 1586, 1305. *If reverse phase column chromatography is not possible then the crude material can be carried forward to the next step with no further purification.*

Methyl 3-((((6-chloro-4-methylpyridin-yl)methyl)methoxy)phosphoryl)methyl) picolinate (43)



Method 1:

To a stirred solution of **55** (413 mg, 1.16 mmol) in toluene:MeOH (7.5 mL, 4:1) at 0 °C was added TMS-diazomethane (1.0 mL of a 2.0 M solution in hexanes, 2.0 mmol) dropwise until the gas stopped evolving. The reaction was warmed to r.t. and

stirred for 0.5 h. The reaction mixture was quenched with excess acetic acid and neutralised with sat. $NaHCO_3$ then extracted with CH_2Cl_2 (x 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an orange oil. The crude material was purified by silica gel flash column chromatography (0 – 10% MeOH in CH_2Cl_2) and the *title compound* was isolated as a yellow oil (215 mg, 50%).

Method 2:

To a stirred solution of **55** (2.08 g, 5.86 mmol) and Cs_2CO_3 (4.13 g, 11.7 mmol) in MeCN (44 mL) was added MeI (0.58 mL, 9.4 mmol). The reaction mixture was heated to 40 °C for 1 h then warmed to 50 °C for 6.25 h. Additional MeI (0.18 mL, 2.9 mmol) was added and the reaction was heated at 50 °C for a further 2 h. The reaction mixture was concentrated *in vacuo*, filtered and washed with CH_2Cl_2. The filtrate was dry loaded onto silica and purified by silica gel flash column chromatography (0 - 10% MeOH in CH_2Cl_2) and the *title compound* was isolated as an orange gum (1.41 g, 65%).

Method 3 (on crude phosphinic acid):

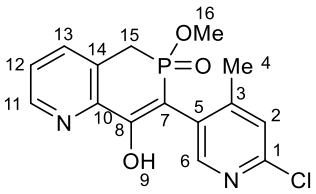
To a stirred solution of ammonium hypophosphite (129 mg, 3.96 mmol) in HMDS (0.83 mL, 4.0 mmol) was heated to 110 °C for 2 h under constant flow of argon. The reaction mixture was cooled to 0 °C and diluted with CH_2Cl_2 (2.0 mL). **47** (874 mg, 3.96 mmol) in CH_2Cl_2 (2.0 mL) was added then the reaction mixture was warmed to r.t. for 16 h. HMDS (3.04 mL, 14.5 mmol) was added and the mixture was held at 0 °C for 2.5 h. **44** (911 mg, 3.96 mmol) in CH_2Cl_2 (2.0 mL) was added and the reaction mixture was warmed to r.t. for 24 h. The mixture was cooled to 0 °C and quenched with MeOH. *The crude material was carried through to the following step with no further purification.*

To a stirred solution of crude **55** (3.96 mmol, assumed 100% yield) in toluene:MeOH (12.0 mL, 4:1) at r.t. was added TMS-diazomethane (4.0 mL of a 2.0 M solution in hexanes, 8.0 mmol). The reaction mixture was stirred for 25 min. The reaction mixture was quenched with excess acetic acid and neutralised with sat. $NaHCO_3$ then extracted with EtOAc (x 3). The combined organic extracts were washed with brine (x 1), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an orange oil. The crude material was purified by silica gel column chromatography (1:9.5:9.5 MeOH:CH_2Cl_2:EtOAc - 2:9:9 MeOH:CH_2Cl_2:EtOAc) and the *title compound* was isolated as a pale yellow oil (143 mg, 10%).

Data:

R_f: 0.39 (5% MeOH/CH_2Cl_2) or 0.14 (1:9.5:9.5 MeOH:CH_2Cl_2:EtOAc); ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.65 (apparent dt, J_{HH} = 4.6, J_{HH} = 1.9 Hz, 1H), 8.14 (d, J_{HH} = 2.7 Hz, 1H), 7.83 (apparent dt, J_{HH} = 8.0, J_{HH} = 1.9 Hz, 1H), 7.45 (ddd, J_{HH} = 8.0, J_{HH} = 4.6, J_{HH} = 0.8 Hz, 1H), 7.15 (s, 1H), 4.00 (s, 3H), 3.87 – 3.67 (m, 2H), 3.48 (d, J_{HP} = 10.6 Hz, 3H), 3.22 – 3.08 (m, 2H), 2.34 (s, 3H), 1.63 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 166.7 (Cq), 150.6 (CH, d, J_{CP} = 5.3 Hz), 150.4 (Cq, d, J_{CP} = 3.7 Hz), 150.1 (Cq, d, J_{CP} = 5.0 Hz), 148.3 (CH, d, J_{CP} = 3.0 Hz), 147.0 (Cq, d, J_{CP} = 5.9 Hz), 140.6 (CH, d, J_{CP} = 4.4 Hz), 129.7 (Cq, d, J_{CP} = 8.5 Hz), 126.5 (CH, d, J_{CP} = 2.6 Hz), 125.7 (CH, d, J_{CP} = 2.9 Hz), 125.5 (Cq, d, J_{CP} = 10.0 Hz), 53.2 (CH_3), 52.5 (CH_3, d, J_{CP} = 7.2 Hz), 33.3 (CH_2, d, J_{CP} = 84.1 Hz), 30.8 (CH_2, d, J_{CP} = 87.9 Hz), 19.7 (CH_3); ^{31}P{^{1}H} NMR (162 MHz, chloroform-*d*) δ 47.0; HRMS (ESI$^+$) $C_{16}H_{19}{}^{35}ClN_2O_4P^+$ $[M+H]^+$ calcd. 369.0765, found 369.0783; IR (ATR) ν_{max} 3048, 2953, 1719, 1586, 1303, 1029.

7-(6-chloro-4-methyl-3-pyridyl)-6-methoxy-6-oxo-5H-phosphinino[4,3-b]pyridin-8-ol (19)



Method 1:

To a stirred solution of **43** (66 mg, 0.18 mmol) in EtOH (2.0 mL, reagent grade) at r.t. was added NaOEt (0.13 mL of a 21 wt% solution in EtOH, 0.36 mmol) dropwise and stirred at r.t. for 3 h. The reaction mixture was quenched with acetic acid, neutralised with sat. $NaHCO_3$, diluted with H_2O and extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with brine (x 1), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid. The crude material was recrystallised with Et_2O, triturated with Et_2O (x 4) and the solvent removed from MeCN/H_2O with a freeze drier and the *title compound* was isolated as a white powder (20 mg, 33%).

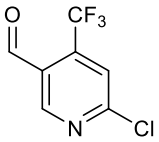
Method 2:

A stirred solution of **43** (1.41 g, 3.82 mmol) and DBU (1.43 mL, 9.55 mmol) in MeCN (34 mL) was heated to 60 °C for 24 h. The solvent was removed *in vacuo* and the residue was dissolved in water. The aqueous solution was acidified to pH 2 – 3 with HCl (2.0 M aqueous solution) and was extracted with EtOAc (x 3). The combined organic extracted were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a residue. The crude material was purified by recrystallisation with hot MeCN then cooled to 4 °C for 3 days. The light brown solid was filtered and washed with ice-cold MeCN, the *title compound* was isolated as an off-white powder (609 mg, 47%).

Data:

The *title compound* was isolated as a mixture of atropisomers (1.3:1); m.p.: 70 – 72°C and 86 – 88°C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.49 (br s, 1H, H - 9), 8.58 – 8.51 (m, 1H, H - 11), 8.48 (d, J_{HP} = 1.7 Hz, 0.43H, *min*or, H - 6), 8.23 (d, J_{HP} = 1.7 Hz, 0.57H, *major*, H - 6), 7.75 – 7.68 (m, 1H, H - 13), 7.42 (ddt, J_{HH} = 7.8, J_{HH} = 4.7, J_{HH} = 1.6 Hz, 1H, H - 12), 7.29 (s, 0.57H, *major*, H - 2), 7.27 (s, 0.43H, *minor*, H - 2), 3.68 (d, J_{HP} = 11.1 Hz, 1.86H, *major*, H - 16), 3.57 (d, J_{HP} = 11.0 Hz, 1.32H, *minor*, H - 16), 3.54 – 3.38 (m, 2H, H - 15), 2.43 (s, 1.84H, *major*, H - 4), 2.33 (s, 1.41H, *minor*, H - 4); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 156.2 (Cq, d, J_{CP} = 23.8 Hz, C - 8), 155.8 (Cq, d, J_{CP} = 23.8 Hz, C - 8), 151.6 (Cq, d, J_{CP} = 3.8 Hz, C - 5), 151.0 (Cq, d, J_{CP} = 1.9 Hz, C - 1), 151.0 (Cq, d, J_{CP} = 1.9 Hz, C – 1), 150.8 (CH, d, J_{CP} = 3.6 Hz, C - 6), 150.4 (Cq, d, J_{CP} = 4.7 Hz, C - 5), 150.1 (CH, d, J_{CP} = 3.6 Hz, C - 6), 146.6 (CH, C – 11), 144.5 (Cq, d, J_{CP} = 11.6 Hz, C - 10), 144.5 (Cq, d, J_{CP} = 11.6 Hz, C - 10), 139.1 (CH, d, J_{CP} = 13.7 Hz, C - 13), 139.1 (CH, d, J_{CP} = 14.5 Hz, C - 13), 127.3 (Cq, d, J_{CP} = 4.5 Hz, C - 14), 127.2 (Cq, d, J_{CP} = 4.5 Hz, C - 14), 126.8 (Cq, C – 3), 126.4 (Cq, C – 3), 125.5 (CH, C – 2), 125.4 (CH, C – 2), 125.3 (CH, C – 12), 125.1 (CH, C – 12), 101.8 (Cq, d, J_{CP} = 135.0 Hz, C - 7), 101.5 (Cq, d, J_{CP} = 135.0 Hz, C - 7), 52.2 (CH_3, d, J_{CP} = 6.4 Hz, C - 16), 52.0 (CH_3, d, J_{CP} = 6.4 Hz, C - 16), 30.7 (CH_2, d, J_{CP} = 95.3 Hz, C - 15), 30.5 (CH_2, d, J_{CP} = 95.3 Hz, C - 15), 20.0 (CH_3, C – 4), 19.6 (CH_3, C – 4); ^{31}P{^{1}H} NMR (162 MHz, chloroform-*d*) δ 35.2 (*minor*), 34.8 (*major*); HRMS (ESI^{+}) $C_{15}H_{14}{}^{35}ClN_2NaO_3P^{+}$ $[M+H]^{+}$ calcd. 359.0323, found 359.0336; IR (ATR) υ_{max} 3444, 3185, 2923, 2850, 1630, 1579, 1461, 1438, 1333, 1221, 1021.

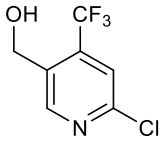
6-chloro-4-(trifluoromethyl)pyridine-3-carbaldehyde (60)[52]



To a stirred solution of 5-bromo-2-chloro-4-(trifluoromethyl)pyridine **59** (2.16 g, 19.8 mmol) in Et_2O (40 mL) was added *n*-BuLi (7.9 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise at –78 °C. The reaction was held at –78 °C for 45 min then DMF (2.61 mL, 33.7 mmol) was added at –78 °C at a rate of 40 mL/h. The reaction was held at –78 °C for 1.5 h then reaction was quenched with sat. NH_4Cl. The Et_2O were removed *in vacuo* and the remaining solution was extracted with CH_2Cl_2 (x 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a dark orange oil. The crude material was purified by silica gel column chromatography (0 - 10% EtOAc in *iso*-hexanes) and the *title compound* was isolated as a pale yellow oil (2.81 g, 68%).

R_f: 0.45 (5% EtOAc in *iso*-hexanes); ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.38 (q, J_{CF} = 5.6 Hz, 1H), 9.09 (s, 1H), 7.71 (s, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform) δ 186.4 (CH), 157.3 (CH), 151.8 (CH), 140.1 (Cq, q, J_{CF} = 35.1 Hz), 126.0 (Cq), 121.7 (Cq, q, J_{CF} = 275.9 Hz), 121.0 (CH, q, J_{CF} = 5.5 Hz); ^{19}F NMR (376 MHz, chloroform) δ ppm -58.8 (d, J_{HF} = 1.4 Hz); HRMS (GC/EI-TOF), $C_7H_3{}^{35}ClF_3NO$ $[M]^+$, calcd. 208.9850, found 208.9849.

(6-chloro-4-(trifluoromethyl)-3-pyridyl)methanol (61)[53]

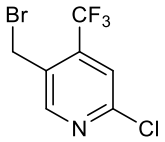


To a stirred solution of **60** (2.86 g, 13.7 mmol) in methanol (55 mL) was added $NaBH_4$ (259 mg, 6.85 mmol) at 0 °C. The reaction was warmed to r.t. and stirred for 1 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (x 3). The

combined organic extracts were washed with brine (x 1), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the *title compound* as an orange liquid (2.61 g, 90%).

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.79 (br s, 1H), 7.56 (s, 1H), 4.93 (d, J_{HH} = 5.5 Hz, 2H), 2.06 (br t, J_{HH} = 5.0 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 151.7 (Cq), 151.1 (CH), 137.6 (Cq, q, J_{CF} = 33.3 Hz), 131.9 (Cq, d, J_{CF} = 1.1 Hz), 122.3 (Cq, q, J_{CF} = 275.2 Hz), 120.4 (CH, q, J_{CF} = 5.5 Hz), 59.1 (CH_2, q, J_{CF} = 8.4 Hz); ^{19}F NMR (376 MHz, chloroform) δ ppm -62.7; HRMS (GC/EI-TOF), $C_7H_5{}^{35}ClF_3NO$, calcd. 211.0006, found 210.9993.

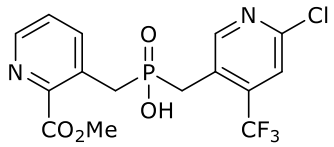
5-(bromomethyl)-2-chloro-4-(trifluoromethyl)pyridine (62)



To a stirred solution of **61** (2.37 g, 11.2 mmol) and PPh_3 (3.52 g, 13.4 mmol) in CH_2Cl_2 (11.0 mL) at 0 °C was added CBr_4 (4.44 g, 13.4 mmol) portion wise. The reaction mixture was warmed to r.t. and stirred for 2 h. The reaction mixture was concentrated *in vacuo* and the crude material was purified by silica gel flash column chromatography (0 – 10% EtOAc in cyclohexane) and the *title compound* to give a pale yellow liquid (2.71 g, 88%).

R_f: 0.36 (10% EtOAc in cyclohexane); ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.64 (s, 1H), 7.57 (s, 1H), 4.58 (s, 2H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 153.8 (CH), 152.3 (Cq), 138.3 (Cq, q, J_{CF} = 32.8 Hz), 129.8 (Cq), 122.0 (Cq, q, J_{CF} = 275.6 Hz), 120.9 (CH, q, J_{CF} = 5.4 Hz), 23.7 (CH_2, q, J_{CF} = 2.1 Hz); ^{19}F NMR (376 MHz, chloroform-*d*) δ -62.2; HRMS (GC/EI-TOF), $C_7H_5{}^{79}Br{}^{35}ClF3N$ $[M]^+$, calcd 272.9162 found 272.9143; IR (ATR) υ_{max} 2922, 1358, 1309, 1288, 1133.

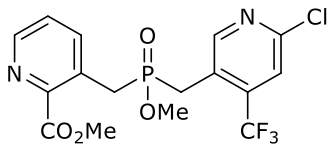
((6-chloro-4-(trifluoromethyl)pyridine-3-yl)methyl)((2-(methoxycarbonyl)pyridine-3-yl)methyl)phosphinic acid (64)



A solution of ammonium hypophosphite (820 mg, 9.87 mmol) and HMDS (2.07 mL, 9.87 mmol) was heated between 100 - 110 °C for 1.5 h under a constant flow of argon. The reaction mixture was then cooled to 0 °C and diluted with CH_2Cl_2 (7.0 mL). **62** (2.71 g, 9.87 mmol) in a solution of CH_2Cl_2 (3.0 mL) was added then the reaction was warmed to r.t. for 18 h. The reaction mixture was cooled to 0 °C and HMDS (2.07 mL, 9.87 mmol) and stirred for 2 h. **44** (2.27 g, 9.87 mmol) in a solution of CH_2Cl_2 (5.0 mL) was added and the reaction was warmed to r.t. and stirred for 18 h. The reaction was quenched with MeOH and concentrated *in vacuo* to give a crude oil. The crude material was purified by reverse phase flash column chromatography (10 – 30% MeCN in H_2O; 0.1% formic acid) and dried using a freeze drier, the *title compound* was isolated a white powder (654 mg, 16%).

m.p.: 80 – 83 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.59 – 8.53 (m, 1H), 8.50 (d, J_{HP} = 2.1 Hz, 1H), 7.68 (apparent dt, J_{HH} = 8.0, J_{HH} = 2.1 Hz, 1H), 7.53 (s, 1H), 7.40 (dd, J_{HH} = 8.0, J_{HP} = 4.6 Hz, 1H), 3.93 (s, 3H), 3.55 (d, J_{HP} = 17.5 Hz, 2H), 3.21 (d, J_{HP} = 16.2 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 166.3 (Cq), 153.5 (CH, d, J_{CP} = 4.9 Hz), 150.9 (Cq, d, J_{CP} = 3.6 Hz), 148.0 (CH, d, J_{CP} = 3.5 Hz), 146.7 (Cq, d, J_{CP} = 6.3 Hz), 141.20 (CH, d, J_{CP} = 4.5 Hz), 139.4 (Cq, qd, J_{CF} = 32.1, J_{CP} = 6.3 Hz), 129.4 (Cq, d, J_{CP} = 8.5 Hz), 126.5 (CH, d, J_{CP} = 2.7 Hz), 124.08 (Cq, d, J_{CP} = 9.0 Hz), 122.0 (Cq, q, J_{CF} = 275.2 Hz), 121.2 – 120.8 (CH, m), 53.2 (CH_3), 33.7 (CH_2, d, J_{CP} = 87.7 Hz), 30.34 (CH_2, d, J_{CP} = 87.4 Hz); ^{19}F NMR (376 MHz, methanol-d_4) δ -62.8; ^{31}P{^{1}H} NMR (202 MHz, chloroform-*d*) δ 44.8; HRMS (ESI$^-$) $C_{15}H_{15}{}^{35}ClF_3N_2O_4P^-$ [M-H]$^-$ calcd. 407.0181, found 407.0190; IR (ATR) υ_{max} 2954, 1726, 1357, 1308, 1289, 1131.

Methyl 3-((((6-chloro-4-(trifluoromethyl)pyridine-3-yl)(methoxy)phosphoryl) methyl) picolinate (65)



Method 1:

To a stirred solution of **64** (100 mg, 0.237 mmol), Cs_2CO_3 (167 mg, 0.474 mmol) in MeCN (2.0 mL) was added MeI (22 μL, 0.36 mmol) at r.t. The reaction was heated to 80 °C for 1.25 h and was then concentrated *in vacuo* to give the crude material. The crude material was purified by silica gel column chromatography (5% MeOH in CH_2Cl_2) to give a bright yellow solid (54 mg, 54%).

Method 2 (on crude phosphinic acid):

A solution of ammonium hypophosphite (947 mg, 11.4 mmol) and HMDS (2.39 mL, 11.4 mmol) was heated at 100 °C for 1.5 h under a constant flow of argon. The reaction mixture was then cooled to 0 °C and diluted with CH_2Cl_2 (9.0 mL). **62** (3.13 g, 11.4 mmol) in a solution of CH_2Cl_2 (2.0 mL) was added then the reaction was warmed to r.t. for 18 h. The reaction mixture was cooled to 0 °C and HMDS (2.39 mL, 11.4 mmol) and stirred for 2 h. **44** (2.62 g, 11.4 mmol) in a solution of CH_2Cl_2 (11.0 mL) was added and the reaction was warmed to r.t. and stirred for 19 h. The reaction was quenched with MeOH and concentrated *in vacuo* to give a crude oil.

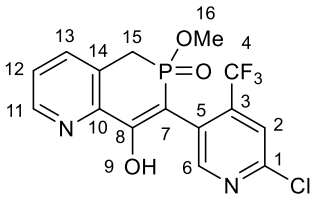
To a stirred solution of crude **64** (11.4 mmol, assumed 100%) and Cs_2CO_3 (12.1 g, 34.2 mmol) in MeCN (86 mL) was added MeI (2.13 mL, 34.2 mmol). The reaction mixture was heated to 80 °C for 1 h, then the solution was concentrated *in vacuo*, filtered and washed with EtOAc. The filtrate was washed with brine (x 1) and the aqueous wash was extracted with EtOAc (x 1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a dark brown oil. The crude material was purified by silica gel column chromatography (5% MeOH in

CH_2Cl_2) to give a brown gum. The material was purified by a second silica gel column chromatography (9.5:9.5:1, CH_2Cl_2:EtOAc:MeOH) and the *title compound was* isolated as an orange gum (682 mg, 14%).

Data:

R_f: 0.13 (5% MeOH in CH_2Cl_2); m.p.: 80 – 83 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.69 - 866 (m, 1H), 8.62 (d, J_{CP} = 2.3 Hz, 1H), 7.83 (apparent dt, J_{HH} = 8.0, J_{HH} = 2.0 Hz, 1H), 7.56 (s, 1H), 7.45 (dd, J_{HH} = 8.0, J_{HH} = 4.7 Hz, 1H), 3.99 (s, 3H), 3.83 – 3.73 (m, 2H), 3.52 (d, J_{HP} = 10.7 Hz, 3H), 3.44 – 3.26 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 166.6 (Cq), 153.6 (CH, d, J_{CP} = 4.7 Hz), 151.2 (Cq, d, J_{CP} = 3.5 Hz), 148.4 (CH, d, J_{CP} = 2.7 Hz), 147.1 (Cq, d, J_{CP} = 6.2 Hz), 140.6 (CH, d, J_{CP} = 4.5 Hz), 139.3 (Cq, qd, J_{CF} = 32.2, J_{CP} = 6.4 Hz), 129.2 (Cq, d, J_{CP} = 9.0 Hz), 126.4 (CH, d, J_{CP} = 2.7 Hz), 123.9 (Cq, d, J_{CP} = 8.9 Hz), 122.1 (Cq, q, J_{CF} = 275.3 Hz), 121.09 (CH, dd, J_{CF} = 6.9, J_{CP} = 4.4 Hz), 53.2 (CH_3), 52.5 (CH_3, d, J_{CP} = 7.2 Hz), 33.2 (CH_2, d, J_{CP} = 85.7 Hz), 30.2 (CH_3, d, J_{CP} = 86.3 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -61.7; ^{31}P{^{1}H} NMR (202 MHz, chloroform-*d*) δ 45.4; HRMS (ESI$^+$) $C_{16}H_{16}{}^{35}ClF_3N_2O_4P^-$ $[M+H]^+$ calcd. 423.0483, found 423.0483; IR (ATR) υ_{max} 3070, 3007, 2948, 2892, 2844, 1721, 1166, 1033.

7-(6-chloro-4-(trifluoromethyl)pyridine-3yl)-8-hydroxy-6-methoxy-5*H*-phosphinino[4,3-*b*]pyridine 6-oxide (66)

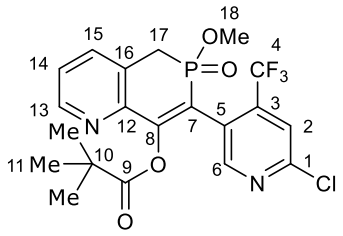


A solution of **65** (665 mg, 1.57 mmol) and DBU (0.59 mL, 3.9 mmol) in MeCN (14.0 mL) was heated to 60 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in H_2O and acidified to pH 3-4 then extracted with EtOAc (x 3). The

combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown solid. The solid was triturated with Et_2O (x 1), EtOAc (x 2) and the solvent was removed *in vacuo* and the *title compound* was isolated as an off-white solid (418 mg, 68%) as a 1:1.2 mixture of atropisomers.

m.p.: 161 – 163 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.44 (br s, 1H, H - 8), 8.68 (s, 0.52H, *major*, H - 6), 8.60 – 8.54 (m, 1H, *major* and *major*, H - 11), 8.46 (s, 0.45H, *minor*, H - 6), 7.76 – 7.73 (m, 1H, *major* and *minor*, H - 12), 7.72 (s, 0.43H, *minor*, H - 2), 7.70 (s, 0.51H, *major*, H - 2), 7.50 – 7.41 (m, 1H, *major* and *minor*, H - 12), 3.74 (d, J_{HP} = 11.2 Hz, 1.34H, *minor*, H - 16), 3.60 (d, J_{HP} = 11.2 Hz, 1.61H, *major*, H - 16), 3.58 – 3.39 (m, 2H, *major* and *minor*, H - 15); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 157.6 (Cq, d, J_{CP} = 61.1 Hz, C - 8), 157.4 (Cq, d, J_{CP} = 62.0 Hz, C - 8), 153.6 (CH, d, J_{CP} = 3.4 Hz, C - 6), 152.5 (CH, d, J_{CP} = 3.7 Hz, C - 6), 152.1 (Cq, d, J_{CP} = 1.7 Hz, C - 1), 152.0 (Cq, d, J_{CP} = 1.5 Hz, C - 1), 146.9 (CH, C - 11), 146.9 (CH, C - 11), 144.4 (Cq, d, J_{CP} = 8.3 Hz, C - 10), 144.3 (Cq, d, J_{CP} = 8.4 Hz, C - 10), 141.4 (Cq, dq, J_{CF} = 32.4, J_{CP} = 4.3 Hz, C - 3), 140.7 (Cq, dq, J_{CF} = 32.4, J_{CP} = 4.3 Hz, C - 3), 139.3 (CH, d, J_{CP} = 14.1 Hz, C - 13), 139.2 (CH, d, J_{CP} = 13.8 Hz, C - 13), 128.0 (Cq, d, J_{CP} = 5.4 Hz, C - 14), 127.4 (Cq, d, J_{CP} = 4.5 Hz, C - 14), 125.9 (CH, C -12), 125.8 (CH, C -12), 124.6 (br CH, C – 5), 124.1 (br CH, C - 5), 122.2 (Cq, q, J_{CF} = 275.5 Hz, C - 4), 122.1 (Cq, q, J_{CF} = 275.5 Hz, C - 4), 122.0 (CH, q, J_{CF} = 5.0 Hz, C - 2), 121.7 (CH, q, J_{CF} = 4.8 Hz, C - 2), 100.1 (Cq, d, J_{CP} = 136.4 Hz, C - 7), 99.9 (Cq, d, J_{CP} = 136.9 Hz, C- 7), 52.3 (CH_3, d, J_{CP} = 6.4 Hz, C - 16), 52.0 (CH_3, d, J_{CP} = 6.4 Hz, C - 16), 31.0 (CH_2, d, J_{CP} = 97.2 Hz, C - 15), 30.3 (CH_2, d, J_{CP} = 96.1 Hz, C - 15); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.5 (*minor*), -62.8 (*major*); ^{31}P{^{1}H} NMR (162 MHz, chloroform-*d*) δ 33.9 (*minor*), 33.7 (*major*); HRMS (ESI^{+}) $C_{15}H_{12}{}^{35}ClF_3N_2O_3P^{-}$ $[M+H]^{+}$ calcd. 391.0221, found 391.0020; IR (ATR) υ_{max} 3055, 3008, 2956, 2850, 1345, 1121, 1066.

7-(6-chloro-4-(trifluoromethyl)pyridine-3-yl)-6-methoxy-6-oxido-5*H*-phosphinino[4,3-*b*]pyridine-8-yl pivalate (67)

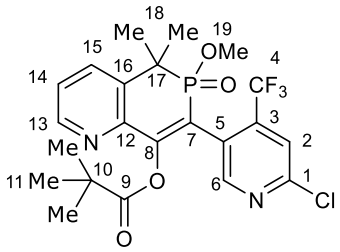


To a stirred solution of **66** (357 mg, 0.914 mmol) and pyridine (0.29 mL, 3.7 mmol) in toluene (11.0 mL) at r.t. was added PivCl (0.23 mL, 1.8 mmol). The reaction mixture was heated to 90 °C for 2 h then cooled to r.t. and quenched with H_2O. The solution was diluted with EtOAc then washed with H_2O (x 1), brine (x 1), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude solid. The solid was purified by silica gel column chromatography (4% MeOH in CH_2Cl_2) to give a white solid. The solid was dried using a freeze drier from MeCN in H_2O and the *title* compound was isolated as a white solid (355 mg, 83%) as a 2:3 mixture of atropisomers. *Material* c*ontains approximately 2%* ***66*** *by* ^{19}F*.*

R_f: 0.17 (4% MeOH in CH_2Cl_2); m.p.: 178 – 181 °C; ^1H NMR (500 MHz, chloroform-*d*) δ 8.56 (s, 0.35H, H - 6, *minor*), 8.55 – 8.51 (m, 1H, H -13, *major* and *minor*), 8.39 (s, 0.6H, H - 6, *major*), 7.69 (s, 0.6H, H - 2, *major*), 7.67 (s, 0.35H, H - 2, *minor*), 7.63 – 7.58 (m, 1H, H - 15, *major* and *minor*), 7.31 – 7.26 (m, 1H, H - 14, *major* and *minor*), 3.72 (d, J_{HP} = 11.2 Hz, 1.9H, H - 18, *major*), 3.61 (d, J_{HP} = 11.2 Hz, 1.2H, H - 18, *minor*), 3.57 – 3.34 (m, 2H, H - 17, *major* and *minor*), 1.13 - 1.02 (m, 9H, H - 11, *major* and *minor*); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 175.2 (Cq, C - 9), 175.1 (Cq, C - 9), 156.7 (Cq, d, J_{CP} = 19.2 Hz, C - 8), 152.7 (CH, d, J_{CP} = 3.5 Hz, C - 6), 152.6 (Cq, d, J_{CP} = 1.5 Hz, C - 1), 152.5 (Cq, d, J_{CP} = 1.5 Hz, C - 1), 151.2 (CH, d, J_{CP} = 3.7 Hz, C - 6), 148.6 (CH, C - 13), 148.5 (Cq, C - 13), 145.6 (Cq, d, J_{CP} = 9.8 Hz, C - 12), 145.4 (Cq, d, J_{CP} = 9.3 Hz, C - 12), 140.46 (Cq, dq, J_{CF} = 32.7, J_{CF} = 3.8 Hz, C - 3), 139.8 (dq, J_{CF} = 32.7, J_{CP} = 3.8 Hz, C - 3), 138.1 (CH, d, J_{CP} = 14.0 Hz, C

-15), 138.0 (CH, d, J_{CP} = 13.7 Hz, C - 15), 127.2 (Cq, d, J_{CP} = 6.3 Hz, C - 16), 126.6 (Cq, d, J_{CP} = 5.9 Hz, C - 16), 124.7 (CH, C - 14), 124.6 (CH, C - 14), 123.5 (Cq, br, C - 5), 123.0 (Cq, br, C - 5), 121.8 (Cq, q, J_{CF} = 275.4 Hz, C - 4), 121.7 (Cq, q, J_{CF} = 275.7 Hz, C - 4), 121.5 (CH, q, J_{CF} = 4.7 Hz, C - 2), 121.0 (CH, q, J_{CF} = 4.8 Hz, C - 2), 119.2 (Cq, d, J_{CP} = 121.0 Hz, C - 7), 118.3 (Cq, d, J_{CP} = 121.0 Hz, C - 7), 52.4 ($2CH_3$, 2d, J_{CP} = 7.0 Hz, C - 18), 39.1 (Cq, C -10), 39.0 (Cq, C - 10), 31.6 (CH_2, d, J_{CP} = 98.7 Hz, C - 17), 30.9 (CH_2, d, J_{CP} = 98.7 Hz, C -17), 26.7 ($3CH_3$, C - 11); ^{19}F NMR (376 MHz, chloroform-*d*) δ -61.5 (*major*), -61.9 (*minor*); $^{31}P\{^1H\}$ NMR (162 MHz, chloroform-*d*) δ 31.8 (*major*), 31.5 (*minor*); HRMS (ESI^+) $C_{20}H_{20}{}^{35}ClF_3N_2O_4P^+$ $[M+H]^+$ calcd. 475.0796, found 475.0786; IR (ATR) υ_{max} 2978, 1750, 1346, 1072, 995.

7-(6-chloro-4-(trifluoromethyl)pyridine-3-yl)-6-methoxy-5,5-dimethyl-6-oxido-5*H*-phosphinino[4,3-*b*]pyridine-8-yl pivalate (68)

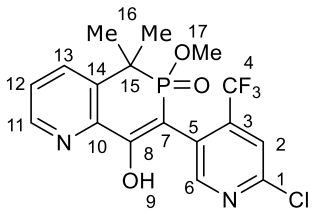


To a stirred solution of **67** (323 mg, 0.680 mmol) in DMF (9.5 mL) at 0 °C was added Cs_2CO_3 (720 mg, 2.04 mmol) portion wise. The reaction mixture was held at 0 °C for 0.5 h then MeI (0.17 mL, 2.7 mmol) was added dropwise. The mixture was warmed to r.t. and stirred for 16 h. The reaction mixture was concentrated *in vacuo* and partitioned between aq. LiCl (5 wt% solution in H_2O) and Et_2O. The biphasic mixture was separated and washed with aq. LiCl (5 wt% solution in H_2O, x 3) then dried $MgSO_4$, filtered and concentrated *in vacuo* to give a crude orange gum. The crude material was purified by silica gel column chromatography (4% MeOH in CH_2Cl_2) to give a white solid. The solid was dried using a freeze drier from MeCN/

H_2O and the *title compound* was isolated a white solid (306 mg, 90%) as a 1:1.4 mixture of atropisomers.

R_f: 0.17 (4% MeOH in CH_2Cl_2); m.p.: 67 - 71 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.54 - 8.43 (m, 1.6H, H - 13, *major* and *minor*, H - 6, *major*), 8.38 (s, 0.4H, H - 6, *minor*), 7.81 – 7.72 (m, 1H, H - 15, *major* and *minor*), 7.70 (s, 0.4H, H - 2, *minor*), 7.66 (s, 0.6H, H - 2, *major*), 7.37 – 7.28 (m, 1H, H - 14, *major* and *minor*), 3.70 (d, J_{HP} = 10.5 Hz, 1.3H, H - 19, *minor*), 3.62 (d, J_{HP} = 10.6 Hz, 1.8H, H - 19, *major*), 1.80 – 1.60 (m, 6H, H - 18, *major* and *minor*), 1.12 – 1.03 (m, 9H, H - 11, *major* and *minor*); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 176.0 (Cq, C - 9), 175.6 (Cq, C - 9), 156.3 (Cq, d, J_{CP} = 18.5 Hz, C - 8), 156.2 (Cq, d, J_{CP} = 19.1 Hz, C - 8), 152.5 (CH, d, J_{CP} = 3.6 Hz, C - 6), 152.5 (Cq, br, C - 1), 152.3 (Cq, br, C - 1), 151.4 (CH, d, J_{CP} = 3.6 Hz, C - 6), 147.8 (CH, C - 13), 147.7 (CH, C - 13), 145.4 (Cq, d, J_{CP} = 9.6 Hz, C - 12), 144.6 (Cq, d, J_{CP} = 9.3 Hz, C -12), 140.3 (Cq, dq, J_{CF} = 33.1, J_{CP} = 3.6 Hz, C - 3), 139.8 (Cq, dq, J_{CF} = 32.7, J_{CP} = 3.6 Hz, C - 3), 139.0 (Cq, d, J_{CP} = 2.7 Hz, C - 16), 138.5 (Cq, d, J_{CP} = 2.7 Hz, C - 16), 132.9 (CH, d, J_{CP} = 9.7 Hz, C - 12), 132.9 (CH, d, J_{CP} = 9.5 Hz, C - 15), 125.1 (CH, C - 14), 125.1 (CH, C - 14), 124.2 (Cq, br, C - 5), 123.7 (Cq, br, C – 5), 122.04 (Cq, q, J_{CF} = 273.7 Hz, C - 4), 121.82 (Cq, q, J_{CF} = 275.8 Hz, C - 4), 121.5 (CH, q, J_{CF} = 4.5 Hz, C - 2), 121.0 (Cq, q, J_{CF} = 4.5 Hz, C - 2), 116.9 (Cq, br, d, J_{CP} = 113.0 Hz, C - 7), 116.0 (Cq, d, J_{CP} = 113.0 Hz, C - 7), 53.4 (CH_3, d, J_{CP} = 6.7 Hz, C - 19), 53.2 (CH_3, d, J_{CP} = 7.4 Hz, C - 19), 39.2 (Cq, C - 10), 39.1 (Cq, C - 10), 37.7 (Cq, d, J_{CP} = 102.5 Hz, C - 17), 37.6 (Cq, d, J_{CP} = 102.5 Hz, C - 17), 26.9 (CH_3, C - 11), 26.8 (CH_3, C - 11), 25.3 (CH_3, C - 18), 24.4 (CH_3, br, C - 18), 19.1 (CH_3, br, C - 18); ^{19}F NMR (376 MHz, chloroform-*d*) δ -61.9 (*minor*), -62.1 (*major*); ^{31}P{^{1}H} NMR (162 MHz, chloroform-*d*) δ 39.7 (*minor*), 39.3 (*major*); HRMS (ESI$^+$) $C_{22}H_{24}{}^{35}ClF_3N_2O_4P^+$ $[M+H]^+$ calcd. 503.1109, found 503.1110; IR (ATR) υ_{max} 2975, 1756, 1348, 1101, 1036.

7-(6-chloro-4-(trifluoromethyl)pyridin-3-yl)-8-hydroxy-6-methoxy-5,5,-dimethyl-5*H*-phosphinino[4,3-*b*]pyridine-6-oxide (57)

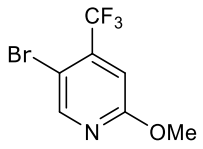


A solution of **68** (138 mg, 0.274 mmol) and LiOH•H_2O (35 mg, 0.82 mmol) in THF:H_2O (1:1, 3.0 mL) was stirred at r.t. for 16 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (x 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude solid. The crude material was purified by silica gel column chromatography (10% MeOH in CH_2Cl_2) and the *title compound* was isolated as a pale yellow solid (54 mg, 47%) as a 1:1 mixture of atropisomers.

R_f: 0.31 (MeOH in CH_2Cl_2); m.p.: 62 – 66 °C and 80 – 84 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.45 (s, 1H, H - 9), 8.63 (d, J_{HP} = 1.5 Hz, 0.5H, H - 6), 8.55 – 8.44 (m, 1H, H - 11), 8.40 (s, 0.5H, H - 6), 7.88 (br d, J_{HH} = 8.0 Hz, 1H, H - 13), 7.70 (s, 0.5H, H -2), 7.67 (s, 0.5H, H - 2), 7.48 (m, 7.55 – 7.40, 1H, H - 12), 3.73 (d, J_{HP} = 10.4 Hz, 1.5H, H - 17), 3.59 (d, J_{HP} = 10.5 Hz, 1H, H - 17), 1.77 – 1.47 (m, 6H, H - 16); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 156.8 (Cq, d, J_{CP} = 20.9 Hz, C - 8), 156.5 (Cq, d, J_{CP} = 21.5 Hz, C - 8), 153.5 (CH, d, J_{CP} = 3.1 Hz, C - 6), 152.3 (CH, d, J_{CP} = 3.5 Hz, C - 6), 151.9 (Cq, C - 1), 151.8 (Cq, C - 1),146.0 (CH, C - 11), 145.9 (CH, C - 11), 143.5 (Cq, d, J_{CP} = 11.1 Hz, C - 10), 143.2 (Cq, d, J_{CP} = 10.8 Hz, C - 10), 141.1 (Cq, dq, J_{CF} = 32.6, J_{CP} = 4.4 Hz, C - 3), 140.5 (Cq, dq, J_{CF} = 32.6, J_{CP} = 4.4 Hz, C - 3), 140.2 (Cq, d, J_{CP} = 1.7 Hz, C - 14), 139.5 (Cq, C - 14), 134.3 (CH, d, J_{CP} = 7.2 Hz, C - 13), 134.3 (CH, d, J_{CP} = 7.2 Hz, C - 13), 126.3 (CH, C - 12), 125.4 (br Cq, C - 5), 124.7 (br Cq, C - 5), 122.3 (Cq, q, J_{CF} = 275.4 Hz, C - 4), 122.2 (Cq, q, J_{CF} = 275.4 Hz, C - 4), 121.9 (CH, q, J_{CF} = 5.0 Hz, C - 2), 121.5 (CH, q, J_{CF} = 4.8 Hz, C - 2), 98.0 (Cq, d, J_{CP} = 125.4 Hz, C - 7), 97.6 (Cq, d, J_{CP} = 127.0 Hz, C - 7),

53.2 (CH_3, d, J_{CP} = 7.3 Hz, C - 17), 53.1 (CH_3, d, J_{CP} = 6.9 Hz, C - 17), 37.9 (Cq, d, J_{CP} = 100.8 Hz, C - 15), 37.7 (Cq, d, J_{CP} = 100.8 Hz, C - 15), 27.0 (CH_3, C - 16), 23.2 (CH_3, d, J_{CP} = 3.1 Hz, C - 16), 22.6 (CH_3, d, J_{CP} = 2.5 Hz, C - 16), 18.4 (CH_3, d, J_{CP} = 4.5 Hz, C - 16); $^{31}P\{^1H\}$ NMR (162 MHz, chloroform-*d*) δ 42.2, 41.5; HRMS (ESI$^+$) $C_{17}H_{16}{}^{35}ClF_3N_2O_4P^+$ $[M+H]^+$ calcd. 419.0534, found 419.0536; IR (ATR) υ_{max} 3207, 3063, 2955, 1646, 1345, 1146, 1034.

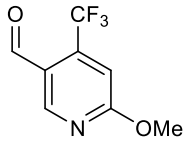
5-bromo-2-methoxy-4-(trifluoromethyl)pyridine (69)[54]



To a stirred solution of 5-bromo-2chloro-4-(trifluoromethyl)pyridine **59** (6.00 g, 23.0 mmol) in MeOH (reagent grade, 58 mL) at r.t. was added NaOMe (1.86 g, 34.5 mmol). The reaction was heated to reflux for 2 h then quenched with H_2O, diluted with brine and extracted with EtOAc (x 4). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* and the *title compound* was isolated as an off white solid (5.03 g, 85%).

m.p.: 54 – 55 °C; ^1H NMR (400 MHz, chloroform-*d*) δ 8.39 (s, 1H), 7.05 (s, 1H), 3.96 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, chloroform-*d*) δ 164.0 (Cq), 151.6 (CH), 140.0 (Cq, q, J_{CF} = 32.9 Hz), 122.0 (Cq, q, J_{CF} = 274.4 Hz), 110.8 (CH, q, J_{CF} = 5.6 Hz), 107.7 (Cq), 54.8 (CH_3); ^{19}F NMR (376 MHz, chloroform-*d*) δ -65.2; HRMS (GC/EI-TOF), $C_7H_5F_3NO$ $[M]^+$, calcd. 254.9507, found 254.9495.

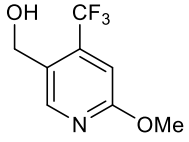
6-methoxy-4-(trifluoromethyl)nicotinaldehyde (70)[55]



To a stirred solution of **69** (4.90 g, 19.1 mmol) in Et_2O:THF (2:1, 173 mL) at –78 °C was added *n*-BuLi (12.6 mL of a 1.6 M solution in hexanes, 19.1 mmol) at a rate of 1 mL/min. The reaction mixture was held at –78 °C for 45 min. DMF (2.07 mL, 26.7 mmol) was added and the reaction mixture was held at –78 °C for 1.5 h then quenched with sat. NH_4Cl. The mixture was warmed to r.t. and the solvent was removed *in vacuo* and the remaining solution was extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with brine (x 2), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow solid. The solid was triturated with ice cold hexane (x 4) and dried *in vacuo*, *the title compound* was isolated as an off-white crystalline solid (3.32 g, 85%).

m.p.: 98 – 100 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 10.22 (q, J_{HF} = 1.9 Hz, 1H), 8.90 (s, 1H), 7.05 (s, 1H), 4.07 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 187.0 (q, J_{CF} = 2.7 Hz), 167.5 (Cq), 152.0 (CH), 140.3 (Cq, q, J_{CF} = 34.5 Hz), 122.3 (Cq, q, J_{CF} = 275.1 Hz), 121.9 (CH), 108.7 (CH, q, J_{CF} = 5.8 Hz), 55.0 (CH_3); ^{19}F NMR (376 MHz, chloroform-*d*) δ -59.7 (d, J_{FH} = 1.8 Hz); HRMS (GC/EI-TOF), $C_8H_6F_3NO_2$ $[M]^+$ calcd. 205.0351, found 205.329; IR (ATR) υ_{max} 3071, 2963, 1685, 1597.

(6-methoxy-4-(trifluoromethyl)pyridine-3-yl)methanol (71)[55]

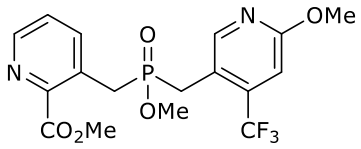


To a stirred solution of **70** (3.29 g, 16.0 mmol) in MeOH (64 mL) at 0 °C was added $NaBH_4$ (303 mg, 8.00 mmol) portion wise. The reaction was warmed to r.t. and

stirred for 1 h. The mixture was then quenched with H_2O and extracted with CH_2Cl_2 (x 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*, the *title compound* was isolated as an off-white crystalline solid (3.27 g, 99%).

m.p.: 70 – 72 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.41 (s, 1H), 6.99 (s, 1H), 4.80 (d, J_{HH} = 5.9 Hz, 2H), 3.98 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 187.0 (CH, q, J_{CF} = 2.6 Hz), 167.5 (Cq), 152.0 (Cq), 140.3 (Cq, q, J_{CF} = 34.3 Hz), 122.3 (Cq, q, J_{CF} = 275.1 Hz), 121.9 (Cq), 108.7 (CH, q, J_{CF} = 6.1 Hz), 55.0 (CH_2); ^{19}F NMR (376 MHz, chloroform-*d*) δ -62.5; HRMS (ESI$^+$) $C_8H_9F_3NO_2^+$ $[M+H]^+$ calcd. 208.0580, found 208.0585; IR (ATR) υ_{max} 3384, 3081, 2962, 2871, 1384, 1130, 1012.

Methyl 3-((methoxy((6-methoxy-4-(trifluoromethyl)pyridine-3-yl)methyl) phosphoryl)methyl)picolinate (74)



To a stirred solution of **71** (3.13 g, 15.1 mmol) in CH_2Cl_2 (30 mL) at r.t. was added PBr_3 (2.13 mL, 22.7 mmol). The reaction mixture was stirred at r.t. for 1.5 h then cooled to 0 °C and quenched with sat. $NaHCO_3$, dropwise. The biphasic mixture was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$ (x 3) and brine (x 1). The combined aqueous washes were then extracted with CH_2Cl_2 (x 2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil (2.14 g). *The material was carried through with no further purification*.

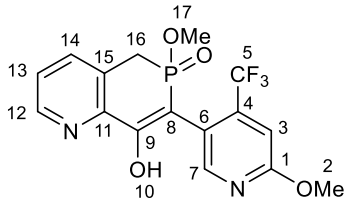
A stirred solution of ammonium hypophosphite (658 mg, 7.92 mmol) in HMDS (1.66 mL, 7.92 mmol) was heated to 110 °C for 1.5 h under a constant flow of argon. The reaction mixture was cooled to 0 °C and diluted with CH_2Cl_2 (5.5 mL) then **72** (2.14 g, 7.92 mmol) was added dropwise in a solution of CH_2Cl_2 (2.5 mL). The reaction

mixture was warmed to r.t. and stirred for 17 h then cooled to 0 °C. HMDS (1.66 mL, 7.92 mmol) was added and the reaction mixture was held at 0 °C for 2 h. **44** (1.73 g, 7.52 mmol) was added as a solution in CH_2Cl_2 (8.0 mL). The reaction mixture was warmed to r.t. and stirred for 20 h. The mixture was quenched with MeOH and concentrated *in vacuo* then triturated with CH_2Cl_2 (x 3) to give an orange gum. *Material carried through crude.*

Three quarters of the crude material (5.94 mmol) was dissolved in MeCN (45 mL) then Cs_2CO_3 (6.28 g, 17.8 mmol) and MeI (1.11 mL, 17.8 mmol) were added and the reaction mixture was heated to 85 °C for 1 h. The mixture was cooled to r.t. and concentrated *in vacuo*, filtered and washed with copious EtOAc. The filtrate was washed with brine (x 1), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. The crude material was purified by silica gel column chromatography (4 – 5% MeOH in CH_2Cl_2) and a second column (1:1:8; MeOH:CH_2Cl_2:EtOAc), the *title compound* was isolated as an orange solid (383 mg, 15%).

R_f: 0.12 (4% MeOH/ CH_2Cl_2) and 0.24 (1:1:8, MeOH/ CH_2Cl_2/ EtOAc); m.p.; 97 – 89 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.69 – 8.60 (m, 1H), 8.38 (d, J_{HP} = 2.6 Hz, 1H), 7.81 (apparent dt, J_{HH} = 7.9, J_{HH} = 1.9 Hz, 1H), 7.42 (dd, J_{HH} = 7.9, J_{HH} = 4.7 Hz, 1H), 6.99 (s, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.90 – 3.60 (m, 2H), 3.50 (d, J_{HP} = 10.7 Hz, 3H), 3.38 – 3.17 (m, 2H); ^{13}C {^{1}H} NMR (126 MHz, chloroform-*d*) δ 166.6 (Cq), 163.7 (Cq), 150.9 (CH, d, J_{CP} = 5.1 Hz), 148.2 (CH, d, J_{CP} = 3.4 Hz), 147.3 (Cq, d, J_{CP} = 6.1 Hz), 140.5 (CH, d, J_{CP} = 4.5 Hz), 139.2 (Cq, qd, J_{CF} = 31.7, J_{CP} = 6.2 Hz), 129.3 (Cq, d, J_{CP} = 9.1 Hz), 126.2 (CH, d, J_{CP} = 3.1 Hz), 122.8 (Cq, q, J_{CF} = 274.9 Hz), 116.2 (Cq, d, J_{CP} = 8.3 Hz), 108.5 (CH, q, J_{CF} = 5.6 Hz), 54.2 (CH_3), 53.1 (CH_3), 52.3 (CH_3, d, J_{CP} = 7.3 Hz), 32.9 (CH_2, d, J_{CP} = 84.7 Hz), 29.6 (CH_2, d, J_{CP} = 88.8 Hz); ^{19}F NMR (376 MHz, chloroform-*d*) δ -62.0; ^{31}P{^{1}H} NMR (202 MHz, chloroform-*d*) δ 46.4; HRMS (ESI$^+$) $C_{17}H_{18}F_3N_2NaO_5P^+$ $[M+Na]^+$ calcd. 441.0798, found 441.0793; IR (ATR) υ_{max} 3041, 2987, 2925, 1718, 1387, 1128, 1020.

8-hydroxy-6-methoxy-7-(6-methoy-4-(trifluoromethyl)pyridine-3-yl-5*H*-phosphinino[4,3-b]pyridine 6-oxide (58)

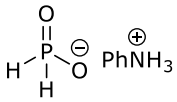


A stirred solution of **74** (350 mg, 0.837 mmol) and DBU (0.31 mL, 2.1 mmol) in MeCN (7.5 mL) was heated to 60 °C for 16 h. Additional DBU (0.13 mL, 0.84 mmol) was added and the reaction was heated for a further 4 h. The reaction mixture was then concentrated *in vacuo* and diluted with H_2O. The aqueous solution was acidified to pH 3 with aq. HCl (1 M) and sat. $NaHCO_3$, then extracted with EtOAc (x 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown gum. A minimum amount of MeCN was added to induce precipitation and the solution was cooled to 0 °C. The solid was the triturated with MeCN (x 1), Et_2O (x 2) at 0 °C to give a white solid (25 mg, 8%). A second batch was obtained from the mother liquor of the triturations which were concentrated *in vacuo* to give an orange solid. The solid was triturated with Et_2O (x 3) and gave the *title compound* as an off-white solid (132 mg, 39%) as a mixture of atropisomers in a ratio of 1:1.2.

m.p.: 161 – 163 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.36 (br s, 1H, H - 10), 8.57 – 8.49 (m, 1H, *major and minor*, H - 13), 8.40 (s, 0.48H, *major*, H - 7), 8.18 (s, 0.42H, *minor*, H - 7), 7.69 (d, J_{HH} = 7.4 Hz, 1H, *major and minor*, H - 14), 7.45 – 7.35 (m, 1H, *major and minor*, H - 12), 7.14 (s, 0.43H, *minor*, H - 3), 7.11 (s, 0.51H, *major*, H - 3), 4.01 (s, 1..63H, *major*, H - 2), 3.99 (s, 1.35H, *minor*, H - 2), 3.72 (d, J_{HH} = 11.1 Hz, 1.34H, *minor*, H - 17), 3.55 (d, J_{HH} = 11.1 Hz, 1.67H, *major*, H - 17), 3.52 – 3.33 (m, 2H , *major and minor*, H - 16); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 164.5 (Cq, C - 1), 164.4 (Cq, C - 1), 157.7 (Cq, d, J_{CP} = 23.0 Hz, C - 9), 156.9

(d, J_{CP} = 24.2 Hz, C - 9), 150.9 (CH, d, J_{CP} = 4.0 Hz, C - 7), 149.5 (CH, d, J_{CP} = 4.0 Hz, C - 7), 146.8 (CH, C - 13), 144.8 (Cq, d, J_{CP} = 9.6 Hz, C - 15), 144.7 (Cq, d, J_{CP} = 9.6 Hz, C - 15), 141.2 (qd, J_{CF} = 31.7, J_{CP} = 3.8 Hz, C - 4), 140.5 (dq J_{CF} = 31.7, J_{CP} = 4.2 Hz, C - 4), 139.14 (CH, apparent t, J_{CP} = 14.0 Hz, C - 14), 128.0 (Cq, d, J_{CP} = 5.4 Hz, C - 11), 127.3 (Cq, d, J_{CP} = 4.5 Hz, C - 11), 125.5 (CH, C - 12), 125.4 (CH, C - 12), 122.7 (Cq, q, J_{CF} = 275.0 Hz, C - 5), 122.6 (Cq, q, J_{CF} = 275.0 Hz, C - 5), 117.4 (Cq, C - 6), 116.8 (Cq, C - 6), 109.5 (CH, q, J_{CF} = 5.2 Hz, C - 3), 108.9 (CH, q, J_{CF} = 5.2 Hz, C - 3), 101.3 (Cq, d, J_{CP} = 137.2 Hz, C - 8), 101.0 (Cq, d, J_{CP} = 137.2 Hz, C - 8), 54.2 (CH_3, C - 2), 54.2 (CH_3, C - 2), 52.1 (CH_3, d, J_{CP} = 6.6 Hz, C - 17), 51.9 (CH_3, d, J_{CP} = 6.6 Hz, C - 17), 31.0 (CH_2, d, J_{CP} = 96.2 Hz, C - 16), 30.2 (CH_2, d, J_{CP} = 95.0 Hz, C - 16); ^{19}F NMR (376 MHz, chloroform-*d*) δ -62.8 (*minor)*, -63.0 (*major)*; ^{31}P{^{1}H} NMR (162 MHz, chloroform-*d*) δ 34.4 (*minor)*, 34.3 (*major)*; HRMS (ESI$^+$) $C_{16}H_{15}F_3N_2NaO_4P^+$ $[M+Na]^+$ calcd. 387.0716, found 387.0715; IR (ATR) υ_{max} 3233, 2956, 2904, 1375, 1157, 1022.

anilinium hypophosphite

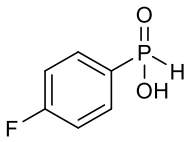


To a stirred solution of hypophosphorus acid (10.8 mL of a 50 wt% solution in H_2O, 100 mmol) at 0 °C was added aniline (9.11 mL, 100 mmol) dropwise. The reaction mixture was allowed to warm to r.t. and stirred for 1 h. Acetone was added until precipitation began then the mixture was cooled to 0 °C until crystals formed. The crystals were filtered and washed with ice cold acetone and the *title compound* was isolated as off-white crystals (7.39 g, 47%).

m.p.: 116 – 118 °C (lit: 113 – 114 °C)[113]; ^{1}H NMR (400 MHz, deuterium oxide) δ 7.58 – 7.47 (m, 1H), 7.43 – 7.37 (m, 1H), 7.01 (d, J_{HP} = 518.7 Hz, 1H); ^{13}C{^{1}H} NMR

(101 MHz, deuterium oxide) δ 130.0 (CH), 129.9 (Cq), 129.0 (CH), 122.8 (CH); ^{31}P NMR (162 MHz, deuterium oxide) δ 7.02 (t, J_{PH} = 518.7 Hz).

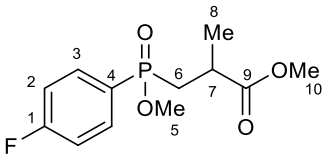
(4-fluorophenyl)phosphinic acid (80)



Anilinium hypophosphite (3.82 g, 24.0 mmol) and Xantphos (378 g, 0.480 mmol) were flushed with N_2 then dissolved in THF (60 mL). NEt_3 (8.36 mL, 60.0 mmol) and 4-bromo-1-fluorobenzene (1.32 mL, 12.0 mmol) were added and the solution was sparged with N_2 for 30 mins. $Pd_2(dba)_3.CHCl_3$ (497 mg, 0.480 mmol) was added and the reaction mixture was heated to reflux for 1 h. The mixture was concentrated *in vacuo* then partitioned between aq. NaOH (1.0 M) and Et_2O. The biphasic mixture was separated and extracted with aq. NaOH (1.0 M, x 2). The extracts were acidified to pH 1 with aq. HCl (3.0 M) and extracted with EtOAc (x 3). The combined organic extracts were washed with brine (x 1), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Cyclohexane was added and the mixture was cooled to –20 °C for 0.5 h to induce precipitation. The excess cyclohexane was removed in *vacuo* and the *title compound* was isolated as a pale yellow solid (1.28 g, 67%).

m.p.: 66 – 68 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.99 – 7.63 (m, 2H), 7.59 (d, J_{HP} = 574.7 Hz, 1H), 7.17 (apparent td, J_{HH} = 8.7, J_{HP} = 2.5 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 165.7 (Cq, dd, J_{CF} = 254.5, J_{CP} = 3.6 Hz), 133.5 (CH, dd, J_{CP} = 13.6, J_{CF} = 9.1 Hz), 126.8 (Cq, dd, J_{CP} = 139.4, J_{CF} = 3.1 Hz), 116.1 (CH, dd, J_{CF} = 21.7, J_{CP} = 15.1 Hz); ^{19}F NMR (376 MHz, chloroform-*d*) δ -104.8 (br s); ^{31}P NMR (162 MHz, Chloroform-*d*) δ 21.5 (d, J_{PH} = 574.7 Hz)*; HRMS (ESI$^+$) $C_6H_5FO_2P^-$ [M-H]$^-$ calcd. 159.0017, found 159.0017; IR (ATR) υ_{max} 3094, 2919, 2850, 2620, 2301, 2121, 1665, 1587, 1497, 1126. *Only J^1 coupling reported.

Methyl 3-((4-fluorophenyl)(methoxy)phosphoryl)-2methylpropanoate (79)

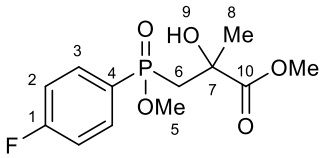


To a stirred solution of **80** (748 mg, 4.67 mmol), $B(C_6F_5)_3$ (84 mg, 0.16), triethylsilane (2.62 mL, 16.4 mmol) in toluene (23 mL) was added methylmethacrylate (2.00 mL, 18.7 mmol). The reaction mixture was heated to 100 °C for 16 h then cooled to r.t. and quenched with MeOH. The solution was concentrated *in vacuo* to give a crude residue. The crude material was dissolved in toluene:MeOH (2.5 mL, 4:1) and cooled to 0 °C then TMS-diazomethane (9.3 mL of a 2.0 M solution in hexanes, 19.0 mmol) was added dropwise. The reaction mixture was warmed to r.t. and stirred for 0.5 h. The mixture was cooled back to 0 °C and quenched with acetic acid (conc.), neutralised with sat. $NaHCO_3$, diluted with brine and extracted with CH_2Cl_2 (x 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow residue. The crude material was purified by silica gel column chromatography (3% MeOH in CH_2Cl_2) and the *title compound* was isolated as a colourless oil (500 mg, 39% over the two steps) as a 1:1 mixture of diastereomers.

R_f: 0.16 (3% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.81 – 7.71 (m, 2H, H - 2), 7.20 – 7.11 (m, 2H, H - 3), 3.63 (s, 1.5H, H - 10), 3.58 (dd, J_{HP} = 11.1, J_{HH} = 0.9 Hz, 3H, H - 5), 3.52 (s, 1.5H, H - 10), 2.96 – 2.85 (m, 0.5H, H - 7), 2.83 – 2.73 (m, 0.5H, H - 7), 2.55 – 2.34 (m, 1H, H - 6), 1.98 (ddd, J_{HP} = 17.3, J_{HH} = 15.3, J_{HH} = 6.8 Hz, 0.5H, H - 6), 1.88 (ddd, J_{HH} = 15.3, J_{HP} = 12.3, J_{HH} = 6.8 Hz, 0.5H, H - 6), 1.28 (dd, J_{HH} = 7.1, J_{HP} = 0.7 Hz, 1.5H, H - 8), 1.22 (d, J_{HH} = 7.1 Hz, J_{HP} = 1.5H, H - 8); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 175.7 (Cq, d, J_{CP} = 10.1 Hz, C - 9), 175.5 (Cq, d, J_{CP} = 10.9 Hz, C - 9), 165.4 (Cq, d, J_{CF} = 253.6 Hz, C - 1), 165.4 (Cq, d, J_{CF} = 254.3 Hz, C - 1), 134.6 – 134.21 (CH, m, C - 2), 126.3 (Cq, dd, J_{CP} = 127.1,

J_{CF} = 3.6 Hz, C - 4), 125.8 (Cq, dd, J_{CP} = 127.3, J_{CP} = 3.2 Hz, C - 4), 116.4 – 115.8 (CH, m, C - 3), 52.0 (CH_3, C - 10), 51.9 (CH_3, C – 10), 51.2 (apparent t, J_{CP} = 6.1 Hz, C - 5), 33.83 (CH, d, J_{CP} = 2.9 Hz, C - 7), 33.8 (CH, d, J_{CP} = 1.8 Hz, C - 7), 33.5 (CH_2, d, J_{CP} = 30.8 Hz, C - 6), 32.7 (CH_2, d, J_{CP} = 30.7 Hz, C - 6), 19.0 (CH_3, d, J_{CP} = 9.1 Hz, C - 8); ^{19}F NMR (376 MHz, chloroform-*d*) δ -105.6 – -105.8 (m); $^{31}P\{^1H\}$ NMR (202 MHz, chloroform-*d*) δ 43.3, 42.7; HRMS (ESI^+) $C_{12}H_{16}FNaO_4P^+$ $[M+H]^+$ calcd. 297.0662, found 297.0660; IR (ATR) υ_{max} 2984, 2951, 1735, 1591, 1208, 1023.

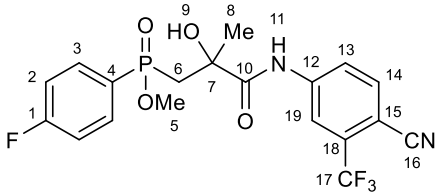
Methyl 3-((4-fluorophenyl)(methoxy)phosphoryl)-2-hydroxy-2-methyl propanoate (89)



To pre-dried glassware under an inert atmosphere a stirred solution of **79** (539 mg, 1.97 mmol) in THF (19.0 mL) at –78 °C was added KHMDS (2.2 mL of a 1.0 M solution in THF, 2.2 mmol). The reaction mixture was held at –78 °C for 45 min then $P(OEt)_3$ (0.68 mL, 3.9 mmol) was added. O_2 was bubbled through the reaction mixture until the yellow colouration dissipated and then the mixture was quenched with HCl (2.0 M aqueous solution) at – 78 °C. The mixture was warmed to r.t. until a homogenous mixture was observed then was extracted with EtOAc (x 3). The combined organic extracts were washed with sat. $NaHCO_3$ (x 1), brine (x 1), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude oil. The crude material was purified by silica gel column chromatography (2% MeOH in CH_2Cl_2) and the *title compound* was isolated as a colourless oil (343 mg, 64%) as a 2:1 mixture of diastereomers.

R_f: 0.13 (2% in MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.85 – 7.73 (m, 2H, *major and* minor, H - 2), 7.26 – 7.16 (m, 2H, *major and minor*, H - 2), 4.59 (s, 0.62H, *major*, H - 9), 4.23 (s, 0.33H, *minor*, H - 9), 3.83 (s, 1.06H, *minor*, H - 11), 3.64 (d, J_{HP} = 11.3 Hz, 2.15H, *major*, H - 5), 3.63 (d, J_{HP} = 11.3 Hz, 1.25H, *minor*, H - 5), 3.51 (s, 2.01H, *major*, H - 11), 2.73 – 2.29 (m, 2H, *major and minor*, H - 6), 1.53 (d, J_{HH} = 2.5 Hz, 2.02H, *major*, H - 8), 1.49 (d, J_{HH} = 2.5 Hz, 1.12H, *minor*, H - 8); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 175.6 (Cq, d, J_{CP} = 4.6 Hz, *minor*, C - 10), 175.1 (Cq, d, J_{CP} = 4.6 Hz, *major*, C - 10), 165.5 (apparent, dt, J_{CF} = 254.2, J_{CP} = 3.1 Hz, *major and minor*, C - 1), 134.4 (CH, dd, J_{CF} = 11.8, J_{CP} = 9.0 Hz, *major*, C - 2), 134.2 (CH, dd, J_{CF} = 12.0, J_{CP} = 8.7 Hz, *minor*, C - 2), 126.7 (Cq, dd, J_{CP} = 130.8, J_{CF} = 3.6 Hz, *minor*, C - 4), 126.1 (Cq, dd, J_{CP} = 130.8, J_{CF} = 3.6 Hz, *major*, C - 4), 116.43 – 115.82 (CH, m, *major and minor*, C - 3), 72.7 (Cq, d, J_{CP} = 5.5 Hz, *minor*, C - 7), 72.5 (Cq, d, J_{CP} = 4.8 Hz, *major*, C - 7), 53.0 (CH_3, *minor*, C - 11), 52.5 (CH_3, *major*, C - 11), 51.3 (CH_3, d, J_{CP} = 6.4 Hz, *minor*, C - 5), 51.2 (CH_3, d, J_{CP} = 6.5 Hz, *major*, C - 5), 39.7 (CH_2, d, J_{CP} = 100.7 Hz, *minor*, C - 6), 39.3 (CH_2, d, J_{CP} = 99.1 Hz, *major*, C - 6), 28.5 (CH_3, d, J_{CP} = 13.6 Hz, *minor*, C - 8), 28.3 (CH_3, d, J_{CP} = 13.6 Hz, *major*, C - 8); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.2 – -105.4 (m, *major*), -105.4 – -105.6 (m, *minor*); ^{31}P{^{1}H} NMR (202 MHz, chloroform-*d*) δ 41.9 (*major and minor*); HRMS (ESI$^+$) $C_{12}H_{16}FNaO_5P^+$ $[M+H]^+$ calcd. 313.0612, found 313.0612; IR (ATR) υ_{max} 3317, 2986, 2953, 2848, 1737, 1199, 1118, 1027.

methyl (3-((4-cyano-3-(trifluoromethyl)phenyl)amino)-2-hydroxy-2-methyl-3-oxopropyl)(4-fluorophenyl)phosphinate (20)



To a stirred degassed solution of **89** (53 mg, 0.18 mmol) and 4-amino-2-(trifluoromethyl)benzonitrile **78** (34 mg, 0.18 mmol) in toluene (3.0 mL) at 0 °C was added $AlMe_3$ (0.32 mL of a 2.0 M solution of hexanes, 0.64 mmol) was added dropwise. The reaction mixture was warmed to r.t. and stirred for 16 h. The mixture was quenched with sat. potassium sodium tartrate and extracted with EtOAc (x 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a crude residue. The crude material was purified by silica gel column chromatography (3% MeOH in CH_2Cl_2) and gave a colourless gum containing 10 wt% CH_2Cl_2. Successive azeotropes with $CHCl_3$ gave a gum containing 20 wt% $CHCl_3$. Successive azeotropes with distilled pentane gave the *title compound* as a white solid (16 mg, 20%) as a 2:1 mixture of diastereomers.

R_f: 0.10 (3% MeOH in CH_2Cl_2); 61 – 63 °C and 68 – 71 °C; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.49 (s, 0.69H, H - 11), 9.24 (s, 0.32H, H - 11), 8.19 (br s, 0.69H, H - 19), 7.96 (br d, J_{HH} = 8.5 Hz, 0.71H, H - 13), 7.88 – 7.54 (m, 3.47H, H - 2, H – 14, H - 13, H 19), 7.26 – 7.22 (m, 0.32H, H - 3), 7.13 – 6.98 (m, 0.65H, H - 3), 6.16 (s, 1H, H - 9), 3.64 (d, J_{HP} = 11.5 Hz, 0.94H, H - 5), 3.56 (d, J_{HP} = 11.4 Hz, 1.78H, H - 5), 2.88 – 2.70 (m, 1.03H, H - 6), 2.49 – 2.19 (m, 1.28H, H - 6), 1.57 (d, J_{HH} = 2.2 Hz, 1.00H, H - 8), 1.49 (br s, 2.00H, H - 8); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 174.1 (Cq, d, J_{CP} = 7.9 Hz, C - 10), 173.6 (Cq, d, J_{CP} = 5.5 Hz, C - 10), 166.0 (Cq, dd, J_{CF} = 256.1, J_{CP} = 3.5 Hz, C - 1), 165.9 (Cq, dd, J_{CF} = 256.1, J_{CP} = 3.2 Hz, C - 1), 141.8 (Cq, C - 12), 141.3 (Cq, C - 12), 136.0 (CH, C - 14), 135.8 (CH, C - 14), 134.5 (CH, dd, J_{CF} = 12.0, J_{CP} = 9.1 Hz, C - 2), 134.3 (CH, dd, J_{CF} = 12.0, J_{CP} = 9.1 Hz, C - 2), 125.3 (Cq, dd, J_{CP} = 131.0, J_{CF} = 3.5 Hz, C - 4), 124.5 (Cq, dd, J_{CP} = 131.0, J_{CF} = 3.5 Hz, C - 4), 122.3 (Cq, q, J_{CF} = 274.2 Hz, C - 17), 122.2 (Cq, q, J_{CF} = 274.2 Hz, C - 17), 121.9 (CH, C - 13), 121.6 (CH, C - 13), 117.4 (CH, q, J_{CF} = 4.7 Hz, C - 19), 117.2 (CH, q, J_{CF} = 4.7 Hz, C - 19), 116.9 (CH, dd, J_{CP} = 21.6, J_{CF} = 14.2 Hz, C - 3), 116.4 (CH, dd, J_{CP} = 21.6, J_{CF} = 14.2 Hz, C - 3), 115.6 (Cq, C - 15), 115.6 (Cq, C - 15), 104.8 (Cq, br, C - 16), 74.7 (Cq, d, J_{CP} = 5.4 Hz, C - 7), 74.1 (Cq, d, J_{CP} = 3.6

Hz, C - 7), 51.9 (CH_3, d, J_{CP} = 6.9 Hz, C - 5), 51.7 (CH_3, d, J_{CP} = 6.4 Hz, C - 5), 37.5 (CH_2, d, J_{CP} = 98.4 Hz, C - 6), 37.0 (CH_2, d, J_{CP} = 98.4 Hz, C - 6), 28.8 (CH_3, d, J_{CP} = 12.6 Hz, C - 8), 28.5 (CH_3, d, J_{CP} = 10.0 Hz, C - 8); ^{19}F NMR (376 MHz, chloroform-*d*) δ -62.2 (*major*), -62.3 (*minor*), -103.6 – -103.7 (m, *major*), -103.7 – -103.8 (m, *minor*); $^{31}P\{^1H\}$ NMR (162 MHz, chloroform-*d*) δ 45.5 (*major*), 44.6 (*minor*); HRMS (ESI^+) $C_{19}H_{18}F_4N_2O_4^+$ $[M+H]^+$ calcd. 445.0935, found 445.0931.

Biological and physical chemistry data:

The potency and physical chemistry data for the analogues synthesised in this section were performed by Syngenta. The pKa values were determined using a Sirius GLpKa apparats. The logP values were determined on a Waters HPLC apparatus using 1 cm or 5 cm packed columns with HiChrom RPB (C8/C18 multi-alkyl phase) coated with HPLC grade octanol, by the comparison of the retention time against a set of standards of known LogP. The EPS (Early Profiling Screen) - glasshouse assay for herbicidal activity was performed as detailed below:

Seeds of a variety of test species were sown in standard sterilised soil in pots. After 8 days cultivation (post-emergence) under controlled conditions in a glasshouse (at 24/16^{o}C, day/night; 14 hours light; 65 % humidity), the plants were sprayed with an aqueous spray solution derived from the formulation of the technical active ingredient in acetone / water (50:50) solution containing 0.5% Tween 20 (polyoxyethelyene sorbitan monolaurate, CAS RN 9005-64-5).

The test plants were then grown under controlled conditions in a glasshouse (at 24/16^{o}C, day/night; 14 hours light; 65 % humidity) and watered twice daily. After 13 days for pre and post-emergence, the test was evaluated visually for percentage phytotoxicity to the plant (where 100 = total damage to plant; 0 = no damage to plant). Plants used: IPOHE (Ipomoea hederacea), ZEAMX (Zea mays), ECHCG

(Echinochloa crus-galli), SEFTA (Setaria faberi), ABUTH (Abutilon theophrasti) and AMARE (Amaranthus retroflexus).

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