Synthesis and Use of Dienyl Phosphates in the Suzuki Coupling

by

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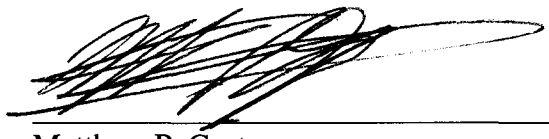
Signature:  8-5-02

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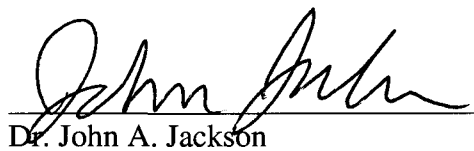 8/5/02

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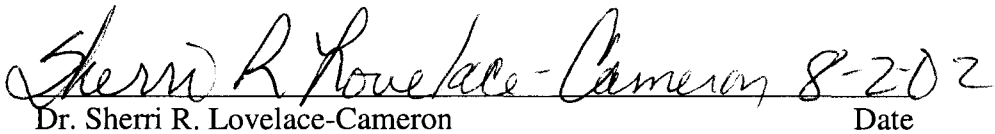

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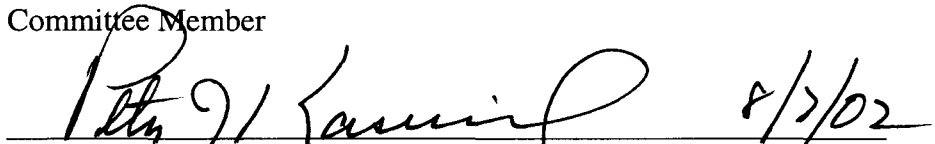 8/7/02

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ABSTRACT

The research presented here is a study of the synthesis of bis(2,2,2-trifluoroethyl) vinyl and dienyl phosphates, and their respective reactivities in two well-known coupling reactions. The required vinyl phosphates can be synthesized by known methods, and this methodology can be extended to dienyl phosphates with only a few slight modifications. Bis(2,2,2-trifluoroethyl) vinyl phosphates are shown to be inadequate starting materials for cross coupling reactions when palladium catalysis is used. Nickel catalysis is shown to be moderately effective as a cross coupling catalyst, providing a methodological basis for the synthesis of new aryl substituted diene systems.

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LIST OF ABBREVIATIONS

Abbreviation	Description
BHT	butylated hydroxytoluene
CaH_2	calcium hydride
d	doublet
ddd	doublet of doublet of doublets
DME	dimethoxyethane
DMF	dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dq	doublet of quartets
eq	equivalent
g	gram
GC	gas chromatography
GC/MS	gas chromatography/mass spectrometry
HMPA	hexamethylphosphoramide
Hz	Hertz
J	coupling constant (in Hz)
LDA	lithium diisopropylamide
M	molar
m	multiplet
mL	milliliter
mmol	millimole
NaH	sodium hydride

n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts-per-million
THF	tetrahydrofuran
TLC	thin layer chromatography

Chapter 1: Introduction

"I'm on it like chickens on a tugboat."
--Brak, "The Brak Show"

"Calm down Tweak; Have some coffee."
--Mr. Tweak, "South Park"

Part 1: Historical Perspective

It is the nature of humanity to strive for perfection; the human condition is not one that takes the concept of mortality lightly. Humans have taken issue with mortality throughout recorded history. Many turned to religion as a way around the transient nature of being, thinking that through life after death one could indeed achieve a certain immortality. Others turned toward the act of actually extending the duration of life itself through various potions and talismans. Indeed, recorded medical history dates back some 4100 years[1] to ancient Mesopotamia. These ancient physicians are in a way the most ancient of chemists, for the act of curing a disease state is nothing more than expressing a particular series of chemical reactions designed to produce a state that is simply thermodynamically favorable to any competing states under the appropriate conditions. Biochemistry has taught us that what humans know as life is really a myriad succession of chemical reactions. The early physicians/chemists of Mesopotamia saw that by affecting a particular reaction in a particular way they could produce a certain result. The Maasai people of Eastern Africa know that the herb they call *Emokotan* (*albizzia anthelminthica*) can be used to treat worm infestation.[2] This information, as well as much more, has been held in the Maasai culture for hundreds of years. This herb, in an oversimplified sense, simply prevents a series of reactions necessary for *in vivo* worm life. Modern medicine has its roots here, and so by extension does modern medicinal

chemistry. Medicinal chemistry is inextricably rooted in organic chemistry because life is an organic phenomenon. So organic chemistry is a science that cannot help but impact virtually every facet of the series of reactions known as life. The conclusion is unavoidable: the curing of disease and the continuance of life arises from organic chemistry. When organic chemistry cannot solve a problem using that which is naturally available, or when the natural product is not available in sufficient quantity, the task is handed to the synthetic chemist. In general, synthetic organic chemistry can be further subdivided into two areas; target-directed synthesis and method-directed synthesis, as illustrated in the "Tree of Organic Synthesis" (**Figure 1**)[3]. Target-directed synthesis is the

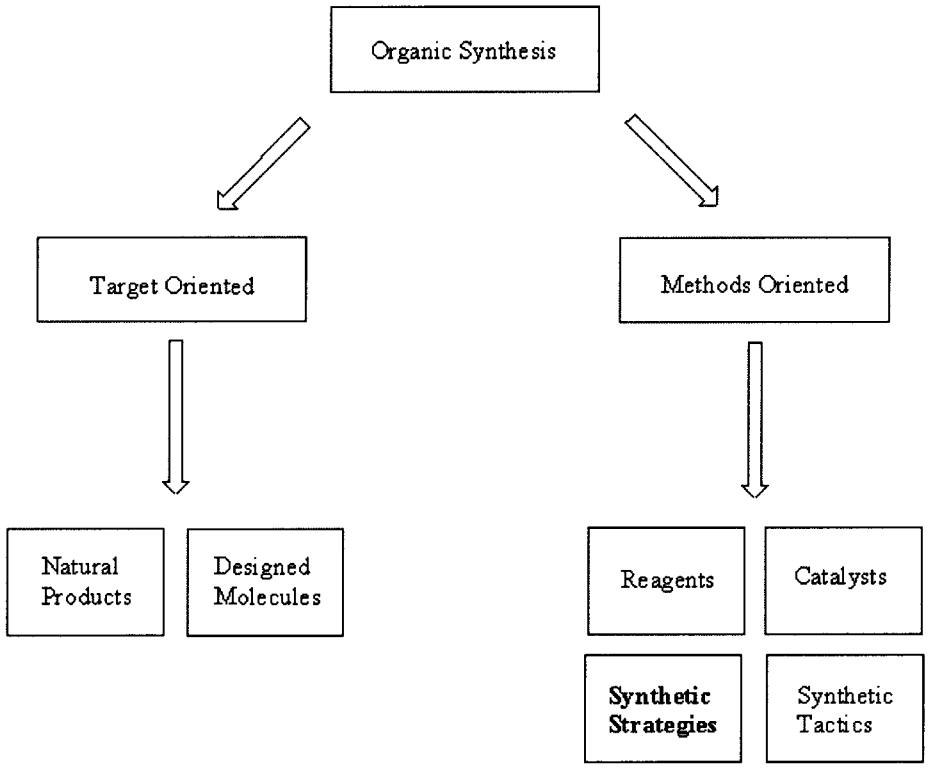


Figure 1

synthesis of larger molecules from smaller molecules with little regard for the methods contained therein, as long as the method performs the desired transformation. Method-directed synthesis, on the other hand, has little concern with the utility of the synthesized product, but more so with the method used to perform that transformation. Dr. K. C. Nicolaou has neatly divided method- directed synthesis into four categories; reagents, catalysis, synthetic strategies, and synthetic tactics.[3] The work presented in this document is primarily of the penultimate type: the development of new synthetic strategies for known transformations, though the work borrows heavily from the other three categories. The known transformations of which modifications were investigated were the Stille coupling and the Suzuki coupling.

Synthetic chemistry is, in its simplest sense, a series of bond-forming and bond-breaking reactions in a coherent order. One of the most valued bonds in synthetic chemistry has always been the carbon-carbon bond, largely because nature has chosen to construct virtually all forms of life out of carbon. Indeed, the scientific community has recognized this and given its highest honor, the Nobel Prize, to several scientists who have delineated new methods towards the formation of carbon-carbon bonds. Of them, the reactions pioneered by Victor Grignard (Nobel Prize with Paul Sabatier, 1912), Otto Diels and Kurt Alder (Nobel Prize, 1950), and George Wittig (Nobel Prize with Herbert C. Brown, 1979) (**Figure 2**)[4] are among the most popular and useful reactions in modern Organic chemistry. These reactions have also succumbed to subsequent modifications;

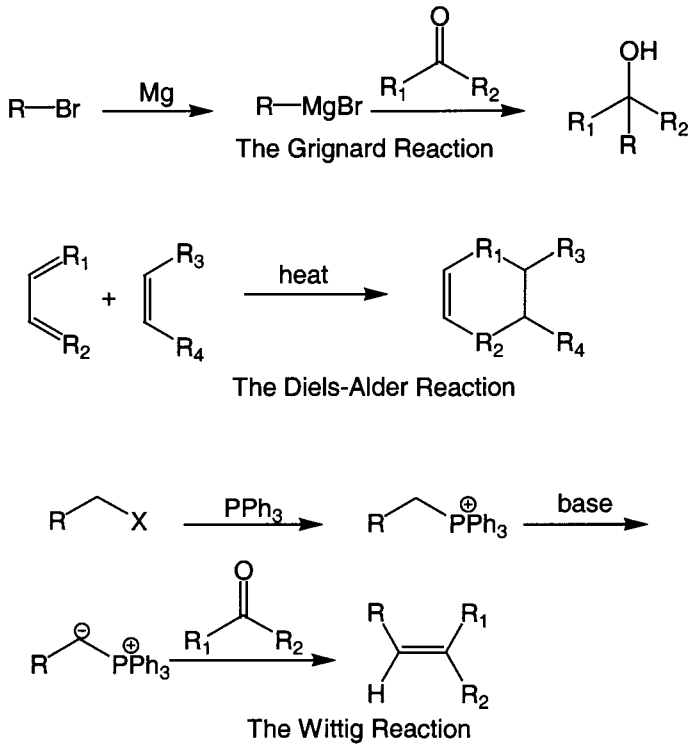


Figure 2

the Horner-Wadsworth-Emmons, or HWE, condensation, a Wittig variant, being one of the most recognizable (**Figure 3**).[5] This reaction is used primarily to synthesize α,β-unsaturated carbonyl compounds.

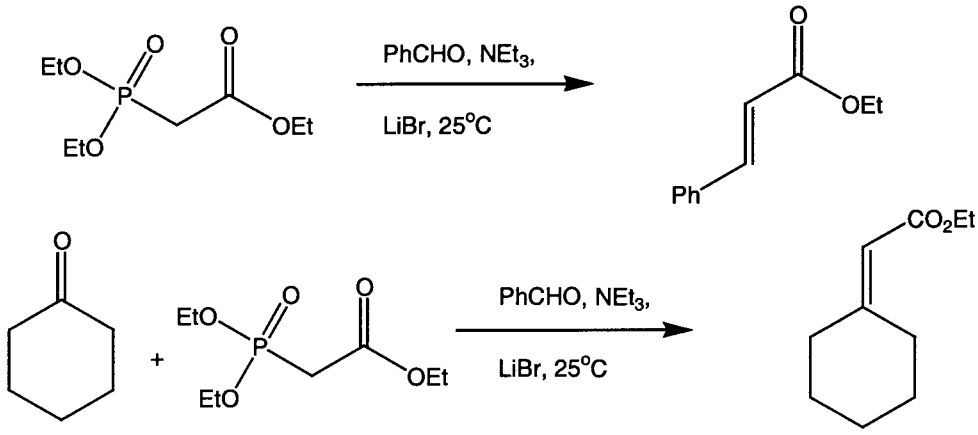


Figure 3

The popularity of the HWE condensation and the parent Wittig reactions illustrate the synthetic utility of phosphorous containing intermediates. This is a point that will become even more evident later. A great deal of the popularity of these reactions (Wittig and HWE) results from the fact that the product contains sp^2 hybrid carbon; an alkene. Alkenes are desirable products for several reasons. Among them are the facts that they are open to several different directions in terms of subsequent functionalization and, that they are present in a great many natural products.

The reactions that an alkene can undergo are indeed numerous (**Figure 4**). Unlike alkanes, which are, for the most part, chemically inert, alkenes provide the synthetic

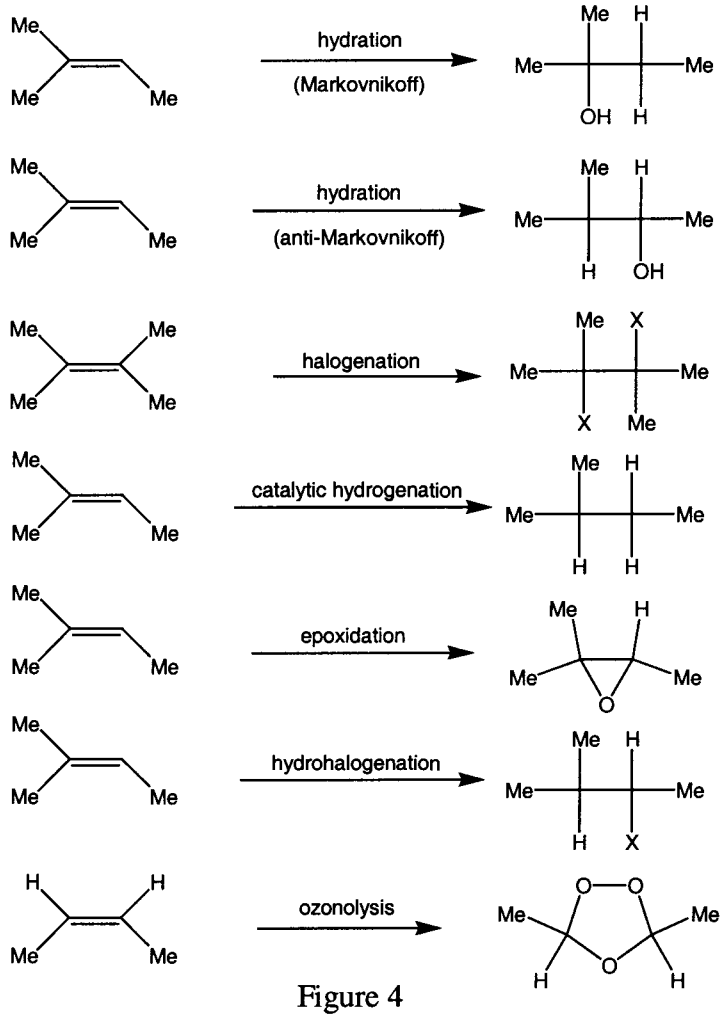


Figure 4

chemist with a "foothold" upon which further transformations can be based. This concept has been belabored on many an undergraduate organic final exam as well as in many a natural product total synthesis; this is another illustration of its importance—it has as much applicability to a beginning student as it does to an experienced scientist.

The total synthesis of a natural product is a long complicated endeavor, the science of which has grown markedly since Wohler's synthesis of urea in 1828.[6] Natural product synthesis received a great tool when the Wittig and HWE reactions were published, both for the fact that the reactions simplified the addition of olefin character to a molecule, but also for the fact that the double bond could be installed unambiguously and then subsequently functionalized to another structural moiety. The wide variety of alkenes that appear in natural product chemistry has made these reactions very useful. These reactions themselves have in truth been put to great use in many natural product total syntheses. Among the more interesting is the use of a Horner-Wadsworth-Emmons condensation in the formation of the C35-C42 fragment (**Figure 5**) of Rapamycin in the course of its total synthesis by Nicolaou.[3] The actual reaction (**Figure 6**) proceeds in a

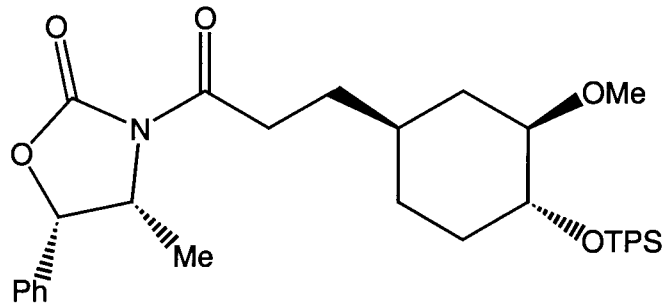


Figure 5

96% yield,[3] and in a 75% overall yield for the remaining steps. Nicolaou's synthesis of Rapamycin utilizes and is illustrative of many types of chemistry, and as intrigued as one might be when examining the steps of the synthesis, such as the HWE condensation

shown above, a pause is unavoidable when one examines the final step. This truly breathtaking piece of chemical ingenuity, a tandem inter-/intramolecular Stille coupling,

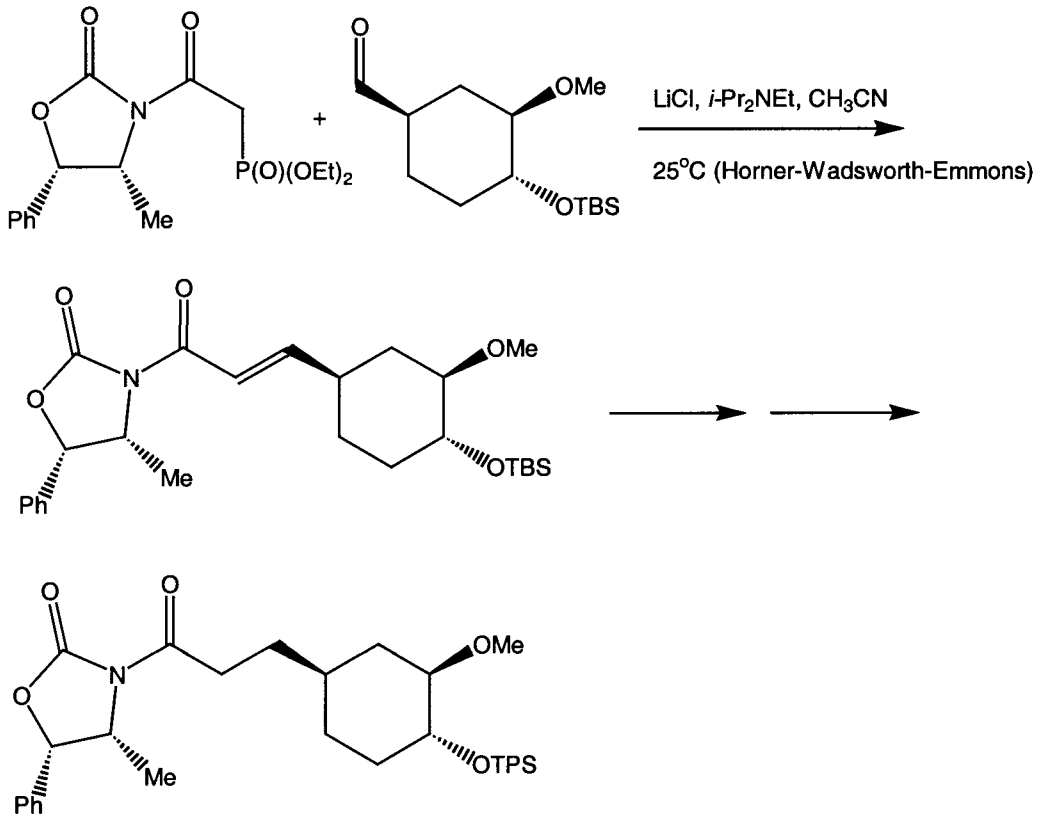


Figure 6

accomplishes the final stitching together of the 31 member macrolide ring[3] at the conjugated *E*-, *E*-, *E*- triene (**Figure 7**). So, in one great step, Nicolaou stitched the ring together and synthesized a particularly tricky structural feature in a stereocontrolled fashion—remarkable work indeed. The Stille Coupling thus appears to be a very powerful synthetic technique. The actual reaction, ingenious as it may be, does suffer from one flaw—the yield of the final product, (-)Rapamycin, is only 27%.[3] The fact that this total synthesis is predicated on a 27%-yielding step is troublesome, for the only way that a compound which has potential biological effects,[3,7] like Rapamycin, is amenable to

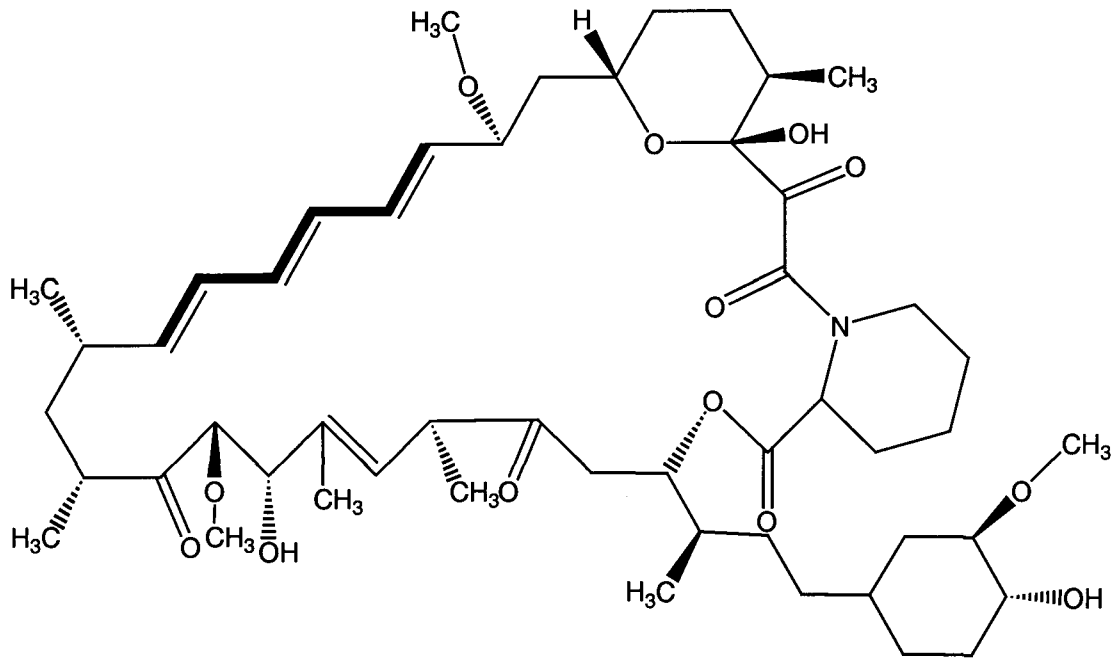


Figure 7

becoming an affordable drug is if its synthesis is efficient and cost-effective. A yield of 27% in an ultimate step becomes a substantial albatross around the neck of a very promising synthesis. At this point, one must either shop elsewhere for an industrial synthesis or modify the methodology of the reaction used in the final step to increase the yield. This is where chemists investigating methodology move to the forefront. As previously stated, there are four possible facets of a reaction that can be modified; reagents, catalysis, synthetic strategies, and synthetic tactics. The research presented here is partly an attempt to modify Stille and Suzuki coupling synthetic strategy through the use of new intermediates. At this point a digression into the chemistry of coupling reactions is necessary.

Part 2: Catalysis

Chemical reactions, much like all dynamic phenomena, occur at certain rates. The hypothetical reaction $A^w + B^x \Im C^y + D^z$ proceeds according some rate *V* which is defined as $V = k\{[A]^l[B]^m[C]^n[D]^o\}$; where [A], [B], [C], and [D] are equilibrium concentrations and *k* is the rate constant. Thermodynamics defines the standard Gibbs' free energy of this hypothetical reaction as proportional to the equilibrium constant: $\Delta G = - RT \ln k_e$, where T is the temperature, R is the gas constant, and the reaction itself is at equilibrium. Reactions whose free energies (ΔG's) are negative are defined to be spontaneous, whereas those with positive values for ΔG are referred to as non-spontaneous. As the value of ΔG becomes more negative, the reaction itself becomes more thermodynamically favorable.

It is important to note, however, that an excessively negative value of ΔG does not necessitate a large value for the rate constant *V*, that is, a thermodynamically favorable reaction is not necessarily a fast reaction. As Christopher Masters so eloquently puts it, "Thermodynamics can tell us a lot about the equilibrium state of systems; it can tell us

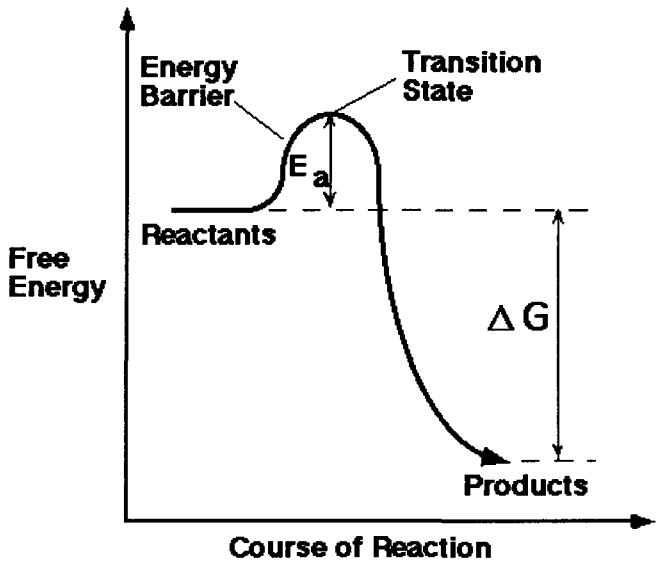


Figure 8

nothing about the speed at which that state is achieved."[8] In organic chemistry, the overall rate of a reaction is dependant on the rate-determining step, or RDS, of that reaction. The RDS is the step that requires the input of energy such that the necessary activation energy (E_a) is met. It is this activation energy that exists as the barrier between products and reactants (**Figure 8**).[9] Were it not for the existence of this barrier, any reaction that was thermodynamically favorable would occur immediately. The reaction of hexane with oxygen which generates carbon dioxide and water, for example, is a favorable reaction in terms of energy. One need not worry excessively about having a bottle of hexane open to the atmosphere, though, as the combustion reaction requires an activation energy that is not likely to be overcome by ambient energetic conditions. Addition of energy in the form of flame to this system will provide the necessary activation energy necessary to cause the reaction to go to equilibrium, which lies so far to the right that the reverse reaction is wholly neglected. The act of increasing the rate of a reaction through affecting a change in the size of the activation energy barrier is known as catalysis. One may loosely consider a spark as the catalyst that sets off the combustion reaction of hexane, though this brutish example will not suffice as the science of catalysis is far more elegant. An actual catalyst is unique in the fact that it accelerates a reaction by participating in the reaction, though it is neither solely a product or a reactant, but rather can be considered to be both, because it is not used up in the reaction. The two qualities a substance must have to be considered to be acting as a positive catalyst, then, are (1) it must have an accelerative effect on the rate of the reaction, that is, $V_{cat} > V_{uncat}$, and (2) it must not be consumed by the reaction.[8] Catalysis can take many forms, and operate in virtually every facet of existence. From the myriad catalytic enzymes in the

body to the mere proton which catalyzes the hydration of an alkene to the catalytic converter which reduces the amount of greenhouse gases exiting the tailpipes of automobiles; catalysts are ubiquitous. One of the aspects of catalysis that has just recently seen a renaissance, though, is the use of transition-metal catalysts, notably palladium, in organic synthesis.

Part 3: Palladium in Organic Synthesis

The use of palladium as a coupling-type catalyst is recognized as having begun in 1958 with the advent of the Wacker process, which produces acetaldehyde from ethylene using palladium (II) chloride and copper (II) chloride as catalysts.[10] (**Figure 9**) This process, which uses a palladium (II) compound as a oxidizing agent, is illustrative of the former of the two types of palladium chemistry; stoichiometric oxidative reactions with palladium (II) compounds. The latter, catalytic reactions, use palladium (0) or palladium (II) compounds in catalytic amounts, usually on the order of 0.5 to 1 mole percent. Of these two types, the reactions of interest are those in which palladium is used catalytically. In the seminal work "Organic Synthesis with Palladium Compounds" Tsuji separates the reactions using palladium as a catalyst into eleven categories. This book, though published some twenty-two years ago, remains a vital reference to the scientist investigating palladium catalysis. It becomes quite clear, however, that in terms of cross

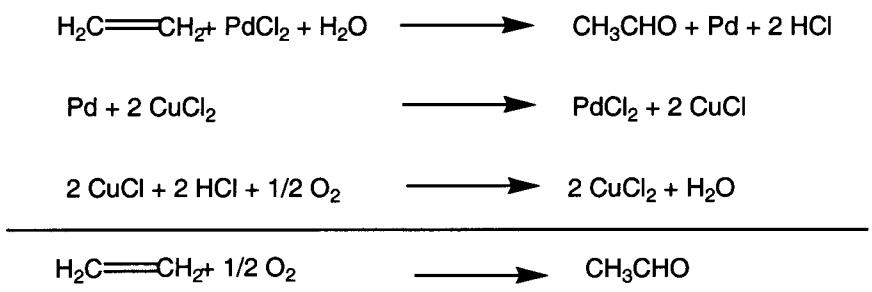


Figure 9

coupling reactions, once the electrophilic capabilities of allyl, aryl, acyl, or alkenyl halides are exhausted, the wealth of available methodology disappears, even in an authoritative work such as Tsuji's. In defense of Tsuji, however, this book was written a few years before palladium-catalyzed cross-couplings experienced its true renaissance. In the early 1980's Trost[11] and others[12] showed the efficacy of allylic sulfonates as coupling partners. A vinyl sulfonate, perhaps derived from a ketone, however, was still out of reach. It was an attempt to fill this apparent hole in the methodological library that led to the development of the Stille coupling in 1984.

In general, coupling reactions are the catalytic combination of reagents into products that cannot be assembled by traditional synthetic routes. Any discussion of coupling chemistry would be incomplete without a brief foray into the Heck reaction discovered in the late 1960's by its namesake, Dr. R. F. Heck.[13] The Heck reaction is a palladium mediated arylation or alkenylation of an alkene (**Figure 10**).[3] It was the Heck reaction that popularized the use of palladium in metathetical catalytic events. This reaction has come to be known as "one of the true 'power tools' in contemporary organic synthesis."[3] The Heck reaction would spawn many analogs; one of the more well-known examples is the Stille coupling.

Part 4: The Stille Coupling

The original Stille coupling was brought into the forefront of synthetic chemistry in 1984 by the late Dr. John K. Stille. Stille showed that vinyl triflates would undergo

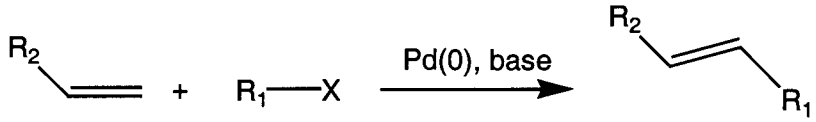


Figure 10

palladium-catalyzed cross-coupling with organostannanes to produce conjugated dienes in good yield[14] (**Figure 11**). R. F. Heck had already shown the viability of palladium-catalyzed coupling of vinyl halides,[15] but up to that point vinyl halides were the only vinyllic species that would act as electrophiles in coupling reactions; a small number considering the number of allylic species that would accomplish the same type of

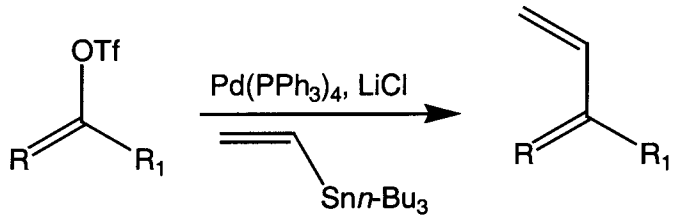


Figure 11

coupling.[3] In order to make cross-coupling reactions more synthetically useful, the number of vinyllic electrophiles had to be increased such that the reaction itself was made more liberal in its scope. To that end, Stille was the first to document insertion of a transition metal into the carbon-oxygen bond of a vinyl sulfonate.[14] This transition metal insertion is the first step of the catalytic cycle (**Figure 12**). Coincident with oxidative addition is the dissociation of two ligands (in the case of tetrakis(ligand)palladium(0) complexes) such that Tolman's sixteen/eighteen electron rule[16] is obeyed. Addition of the carbon-X bond (X= halide, sulfonate, phosphate) to the 14 electron palladium(0) complex which remains yields a 16 electron palladium (II) complex, which then participates in a transmetalative event with the trialkyl vinylstannane, resulting in an exchange of X for the vinyl group. Once isomerized (*trans* to *cis*), reductive elimination of the product returns the catalyst to its fourteen electron ground state, where it enters the catalytic cycle again. At this point it is worth noting that the Stille coupling actually comprises two

different reaction pathways; the direct coupling reaction, which is the reaction of interest, and a carbonylative coupling, which contains an additional step in the catalytic cycle and

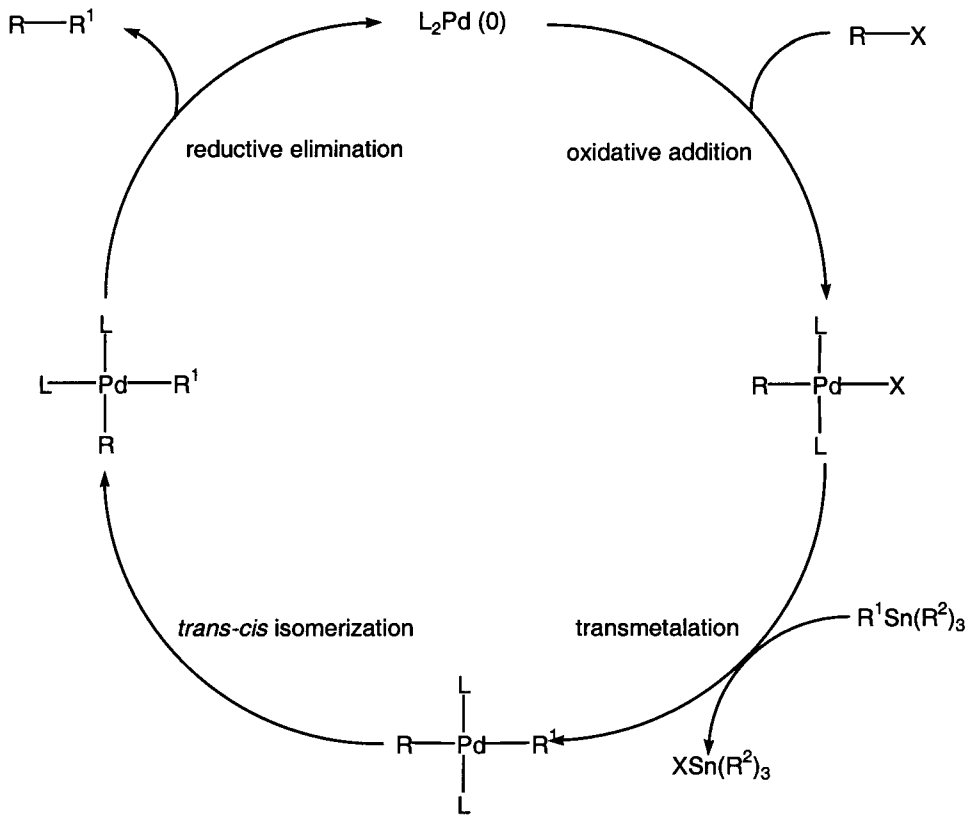


Figure 12

results in a carbonyl bridge between R and R_1, instead of the direct connection described above. To promote a carbonylative-type Stille coupling, one need only allow carbon monoxide to be present as a reactant. The final product of this type of coupling is a ketone (**Figure 13**).[3]

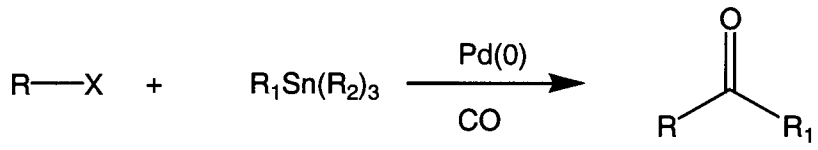


Figure 13

The Stille coupling is a powerful reaction that has seen application in many schemes, not the least of which is the aforementioned use in Nicolaou's Rapamycin synthesis. Additionally, it has been utilized in Evans' synthesis of (+)-A83543 (lecidipin) aglycon[17] and Han and Wiemer's (+)jatrophone synthesis,[18] not to mention Stille's synthesis of pleraplysillin-1.[14]

The Stille coupling was an excellent development in synthetic chemistry, but it is not without it shortcomings. These are largely centered on the trifluoromethane sulfonate ("triflate") intermediates, which have been widely shown[19, 20, 21] to be quite costly as well as somewhat unstable. Additionally, separation of the triflate product from the byproduct of the reaction is somewhat tedious and difficult.[22] Nicolaou noted these problems and showed[21] that cyclic ketene acetal phosphates (lactone vinyl phosphates) offered attractive alternatives as reagents in the Stille coupling to triflates in terms of enhanced stability and lower cost. This remains one of the preeminent modifications of the Stille coupling (**Figure 14**). Yang and Nan noted[19] that excess phosphorylating reagent was trivial to separate from the reaction mixture, thereby eliminating the separation difficulties inherent to triflates. Nicolaou also noted that many different electrophiles

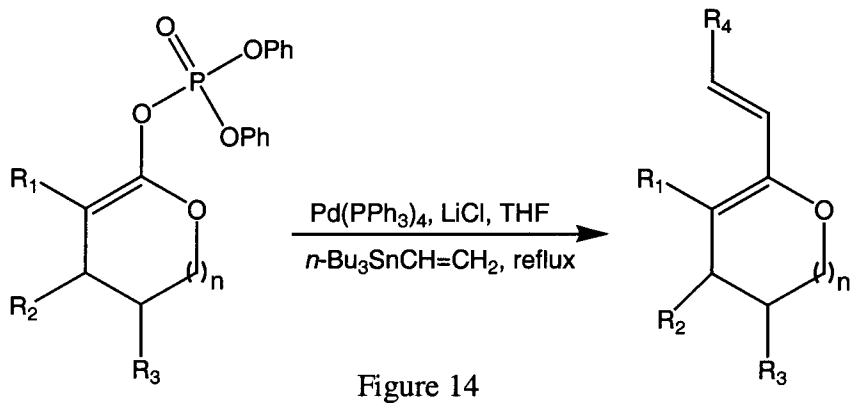


Figure 14

could be used in this coupling process, though he made it clear he believed that diphenyl vinyl phosphates should be the "substrates of choice"[21] for Stille couplings. Much like Wittig's reaction in years past, Stille's was being modified to its benefit by the methodologist sect. The Stille coupling reaction would not be the last to be improved by the use of diphenyl vinylphosphates, though, as there was another coupling reaction simultaneously gaining acclaim. The Stille coupling offered mild reaction conditions, stereocontrol, a high degree of tolerance for other functional groups present, and a limited amount of steric concerns. Unfortunately, there was no way to circumvent the extreme toxicity of the required stannanes. That is, unless a scheme could be designed which required conditions and reagents which were substantially more benign. In actuality, this scheme had already been published.

Part 5: The Suzuki Coupling

Boron chemistry has been an integral part of organic synthesis for some time, due in most part to the efforts of H. C. Brown, who was presented with a Nobel Prize (with Wittig, 1979) in recognition of the advances made through the chemistry he pioneered. Not surprisingly, it was a scientist who had spent time as a postdoctoral research associate in Brown's lab that brought boron chemistry into the realm of the coupling reaction. Akira Suzuki published a landmark paper in 1982 detailing the union of an organic electrophile (in this case a vinyl halide)with an organoboron under palladium catalysis to yield a conjugated diene[23] (**Figure 15**). Moreover, Brown's hydroboration

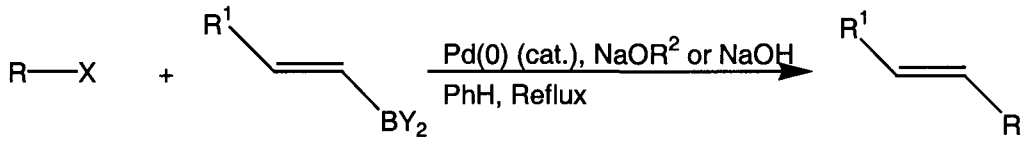


Figure 15

chemistry showed that the required dialkyl organoboron derivatives could be generated regiospecifically[24, 25] (**Figure 16**). The Suzuki coupling has become one of the most

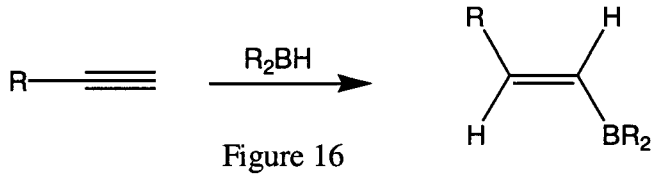


Figure 16

Utilized schemes in synthetic organic chemistry, due to the many benefits it offers the synthetic chemist. Like the Stille coupling, the Suzuki coupling offers a high degree (>98% stereoisomeric purity) of stereochemical retention, mild reaction conditions, and functional group tolerance. However, the Suzuki coupling does not rely on the use of notoriously toxic tin compounds. The catalytic cycle also varies (**Figure 18**); the Suzuki coupling requires the use of a base to affect a methathetical displacement of the halide, phosphate, or sulfonate after oxidative addition, whereas the Stille coupling relies on a simple transmetalative event to remove the electrophilic portion of the starting material. Since the transmetalative step is typically rate-determining, the Suzuki coupling offers additional rate controllability due to the wide variation of reactivity of available bases. It has been shown by Electrospray Ionization Mass Spectrometry (ESI)[26] that if the reaction is run without base present, the catalytic cycle will revert to its former structure (**Figure 13**), with boron acting as the transmetalating agent in lieu of base induced metathesis. This metathetical displacement provides one of the byproducts of the reaction, which is usually inorganic in nature, and is therefore trivial to separate from the reaction mixture. These byproducts are also much less environmentally damaging than their Stille coupling

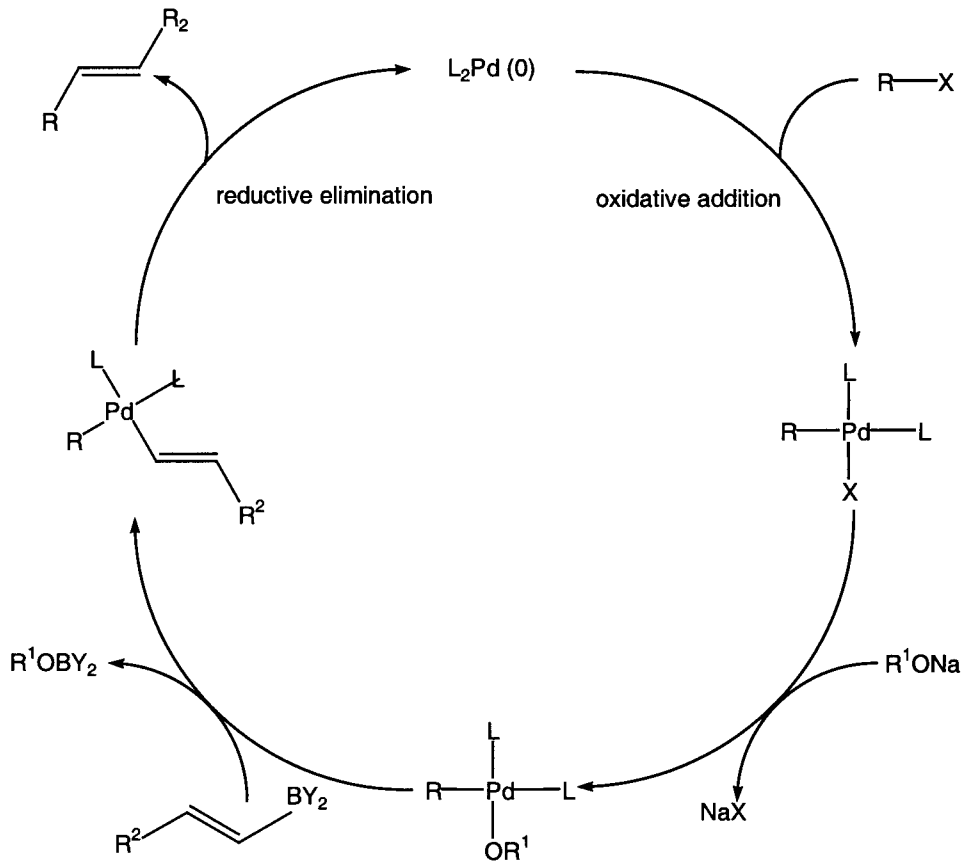


Figure 17

tin counterparts. Also, the Suzuki coupling is, in its purest form, not appreciably water sensitive; aqueous bases (sodium hydroxide, alkoxides) are used quite often. In fact, water has been employed as a solvent in several Suzuki couplings.[27] The synthetic chemist, then, need not be extremely concerned about using air-sensitive techniques, which usually increase the temporal and financial demands of a transformation. Suzuki's reaction is a very user-friendly reaction that has seen much use, both in its original from and in modified form. The modifications themselves are many, though none stray too far from the original.

Of all the iterations of the Suzuki coupling that are present in organic synthesis,

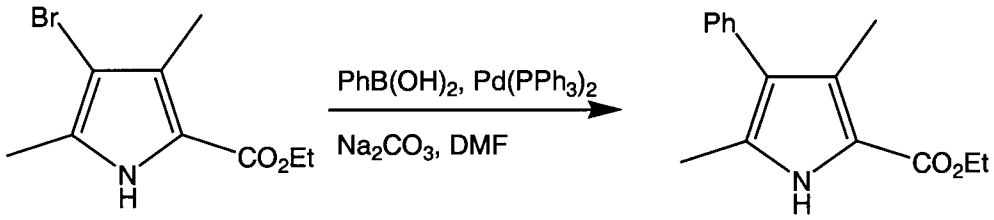


Figure 18

the majority are routes toward the synthesis of conjugated dienes. There are, however, a number of reported syntheses of biaryls through coupling of an arylboronic acid with a haloarene. Chang and Bag have reported the synthesis of a phenylpyrrole from a bromopyrrole (**Figure 18**) in a near quantitative yield in the course of a synthesis of a porphyrin.[28] This reaction proceeds in good yield with no additional ligands. The traditional problem with homogeneous catalysis is separating the catalyst, product and

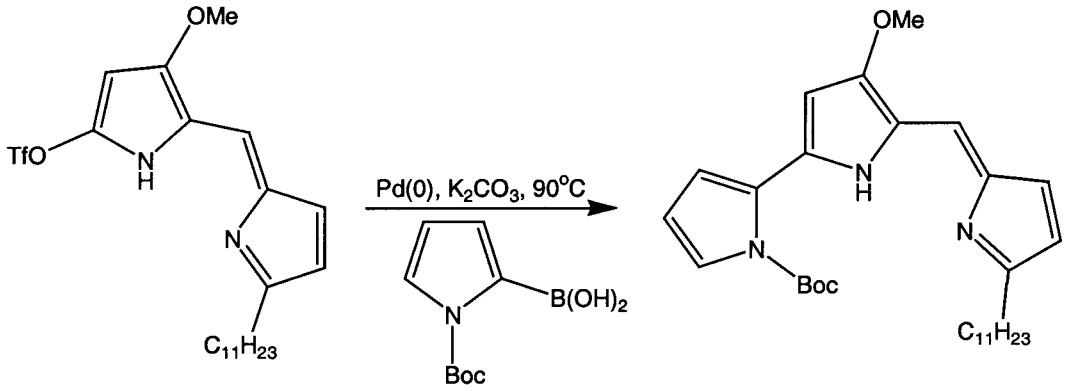


Figure 19

accessory ligands in order to recycle the catalyst. Beller *et. al.* demonstrated the utility of a biphasic catalyst which catalyzes Suzuki couplings between haloarenes and arylboronic acids to produce biaryls in good yield and allows for easy separation and recycling of the catalyst.[29] D'Alessio and Rossi demonstrated an interesting Suzuki variant by producing undecylprodigiosine (a biaryl, **Figure 19**) thorough a Suzuki coupling between an aryltriflate and a protected arylboronic acid.[30]

The use of triflates draws another interesting parallel between the Stille and Suzuki coupling—triflates as electrophiles. As previously mentioned, the problems with triflates had been well documented and subsequently circumvented through the use of Nicolaou's diphenyl vinylphosphate modification. It was literally only a matter of time before diphenyl vinylphosphates would find their way into the Suzuki coupling. In 1999, Nan and Yang introduced a Nickel catalyzed Suzuki coupling between a diphenyl vinylphosphate and phenylboronic acid,[19] yielding a series of aryl substituted olefins (**Figure 20**). They also noted the failure of palladium to successfully catalyze the coupling, presumably due to a deficiency in activity. Coincident with this discovery was an improvement in the synthesis of a bis(trifluoroethyl)phosphorochloridate, which was

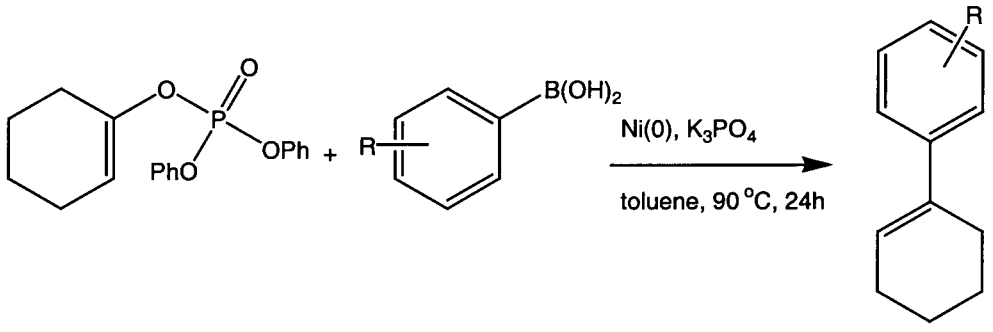


Figure 20

seen to be a potential electrophilic similar in structure to diphenylchlorophosphate.

Part 6: Bis(2,2,2-trifluoroethyl)phosphorochloridate

Triflates have long been known to be effective electrophiles, due to the presence of three fluorines in the molecule. They also have been somewhat maligned for their instability. Despite the problems, they have been shown to be effective as coupling partners. This is not surprising when one considers the fact that coupling reactions by nature require electrophiles as one of the partners. It did not take long after the introduction of diphenyl phosphate methodology for the use of triflates to be shelved by many in favor of Nicolaou's "substrates of choice." A Hartree-Fock (3-21G*) calculation of dipoles in the two competing molecules bound to identical substrates reveals a reasonable difference in dipole magnitude (**Table 1**). Since elementary organic chemistry tells us that "partial charge separation...allows us to make predictions about (its) reactivity,"[32] and a dipole is nothing more than a measurement of partial charge separation, one can roughly predict the relative reactivities of these three compounds as increasing in order of increasing dipole moment. Based on this, bis(2,2,2-trifluoroethyl)

Compound	**Level of Theory**	**Dipole Moment** (debye)
$(C_6H_9)OS(O)_2CF_3$	3-21G*	1.876
$(C_6H_9)OP(O)(OTFE)_2$	3-21G*	6.422

Table 1

vinyl phosphates appeared to be worthy candidates for coupling chemistry. However, the phosphorylating reagent was difficult to synthesize. The only existing literature preparation in the early 1990's was published by Sellars in 1956,[31] and required the addition of phosphorous oxychloride to 2,2,2-trifluoroethanol (**Figure 21**), followed by a

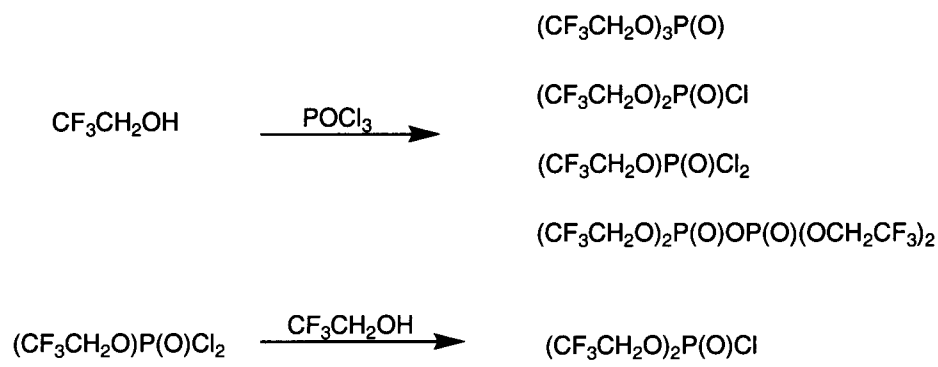


Figure 21

series of high vacuum distillations. This method was shown[32] to be tedious as well as impractical. A new, improved synthesis appeared soon after,[33] wherein the phosphorochloridate was synthesized in a one-pot, near-quantitative reaction scheme (**Figure 22**). Since this preparation was published, several[34] other preparations have surfaced, many with similar yields. The improved preparation of the phosphorylating reagent made the efficient synthesis of bis(trifluoroethyl) vinyl phosphates a distinct possibility.

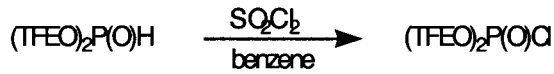


Figure 22

Part 7: Vinyl and Dienyl phosphates

Tautomerization between ketone and enol conformations (**Figure 23**) is a well known phenomena that is exploited extensively in organic synthesis. A simple temperature change is sufficient to force the equilibrium between the two states in the desired direction. Since the ketone form is more stable (for non-aromatic systems) due to

the overall bond strength being higher (~+18 kcal/mol), it is the thermodynamic form; the form that predominates at equilibrium. The science of organic synthesis has developed

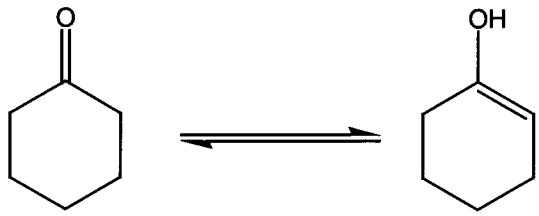


Figure 23

Kinetic Control	**Thermodynamic Control**
Low Temperature	High Temperature
Aprotic Solvent	Protic Solvent
Large, Strong, Hindered Base	Small, Weak Base
Excess Ketone	Quantitative Ketone

Table 2

methods to ensure which form predominates; these are summarized in **Table 2**. Indeed, in cases where enolates are derived from ketones or enones, the bases used are large powerful bases,[19, 20, 21, 32, 35] with lithium diisopropylamide the most common, and the reactions are performed at low temperature, usually in a dry ice/acetone (-78 °C) bath. Stock[32] and Oyeamalu[36] have synthesized these vinylphosphates *via* the kinetically

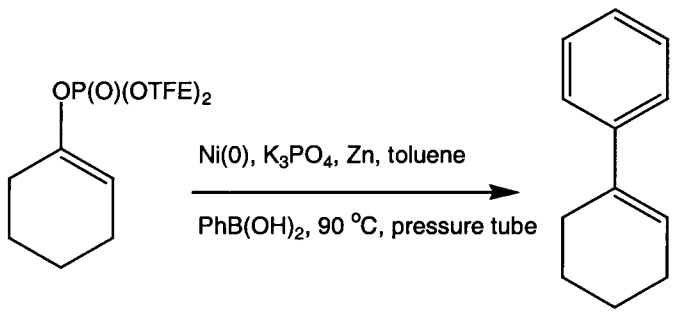


Figure 24

favored enolates of various ketones, and Oyeamalu has shown these vinylphosphates to be viable in a Nickel-catalyzed variant of the Suzuki coupling (**Figure 24**), albeit in moderate yields.

Part 8: Statement of Purpose

It has been shown that diphenyl vinylphosphates are useful as substrates in the Stille coupling,[21] and that bis(2,2,2-trifluoroethyl) vinylphosphates possess, in general, stronger dipole moments than the analogous triflates, such that their action as electrophiles in the Stille coupling should be viable, as well as efficient. It has also been shown that vinylphosphates are viable as substrates in the Suzuki coupling[19] and that lactones and enones can be derivatized to vinyl- and dienylphosphates through similar methodology. It should then be possible to pass lactone and enone derived bis(2,2,2-trifluoroethyl) vinyl- or dienylphosphates through the Suzuki coupling to form new carbon-carbon bonds.

Chapter Two: Results and Discussion

Part 1: Vinylphosphates in the Stille coupling.

The initial focus of this research was the synthesis of vinylphosphates containing the bis(2,2,2-trifluoroethyl) group, then determining their reactivity in the Stille coupling (**Figure 25**).

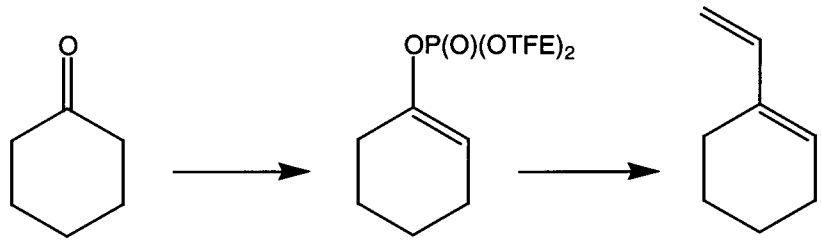


Figure 25

2.1.1: Synthesis of bis(2,2,2-trifluoroethyl) phosphorochloridate **1**

The initial step was to synthesize the electrophile bis(2,2,2-trifluoroethyl) phosphorochloridate by the method developed by Jackson.[33] In this manner bis(2,2,2-trifluoroethyl) phosphorochloridate was synthesized from bis(2,2,2-trifluoroethyl) phosphite *via* sulfuryl chloride in benzene (see **Figure 24**) with no deviation from experimental procedure. High vacuum distillation yielded bis(2,2,2-trifluoroethyl) phosphorochloridate (**1**) in 88% yield.

The ^{13}C NMR spectrum of **1** shows a pair of doublet of quartets (dq). These peaks are resultant from ^{13}C (spin ½) coupling to three ^{19}F (spin ½) and one ^{31}P (spin ½) nuclei. Spectra will be discussed in greater detail in part 4.

2.1.2: Synthesis of vinylphosphates – **2**, **3**, **4**, **6**

After phosphorylating reagent **1** was synthesized, the next step was to synthesize a series of vinylphosphates *via* their ketone enolates (**Figure 26**). Previously, Stock[32] and

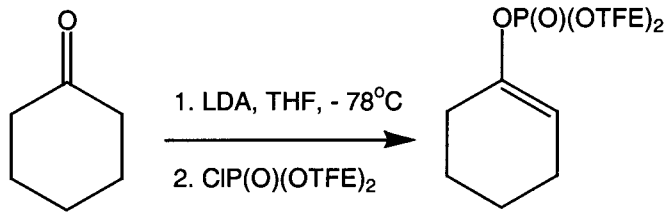


Figure 26

Oyeamalu[36] had synthesized these compounds, but the reported yields were low enough such that a review of the method was necessary. The general procedure that had been used up to this point is as follows: a solution of LDA (5.5 mmol) was prepared *in situ* from diisopropylamine (0.77 mL) and *n*-butyllithium (3.75 mL of a 1.6M solution in hexane), in anhydrous tetrahydrofuran (THF, 20 mL) at –78 °C. To this solution was added dropwise 5.0 mmol of neat ketone. To the solution of the ketone enolate at –78 °C was added neat bis(2,2,2-trifluoroethyl) phosphorochloridate (6 mmol, 0.97 mL) in a dropwise fashion. Once the addition was finished, the reaction mixture was allowed to warm to room temperature while being stirred over a period of 24 hours. Cyclo-pentanone, cyclohexanone, and cycloheptanone were used as representative of 5, 6, and 7 membered cyclic ketones.

Yields for **2**, **3**, and **4** were disappointing at 40-60% by gas chromatography (GC). Also formed in these reaction mixtures were substantial amounts of phosphoramide **5**, which is a byproduct resulting from the nuclephilic substitution at phosphorous (the $S^NP(V)$ mechanism) by LDA (**Figure 27**). In order to increase vinyl phosphate yields, several steps were taken. The first modification was distillation of the ketone starting

materials, as any impurities would tend to reduce yields. This did not have an appreciable effect on yield. The second modification was addition of co-solvents to increase the reactivity of the oxyanion through separation of the oxygen-lithium ion pair. Hexamethylphosphoramide and 12-crown-4 were used as lithium coordinating agents. This modification did not increase yields appreciably either. The third modification was changing the solvent from THF to diethyl ether to decrease the basicity of LDA in an attempt to impart selectivity. This, again, did not increase yield appreciably. A sixth iteration of the three model ketones wherein the LDA was allowed to warm to room temperature to ensure complete deprotonation of diisopropylamine (quantitative formation of LDA) yielded similar results. A seventh iteration where the ketone/LDA mixture was also allowed to warm to room temperature and recooled before addition of the phosphorochloridate was added was then attempted, in an effort to minimize formation of the phosphoramide byproduct. This modification provided an

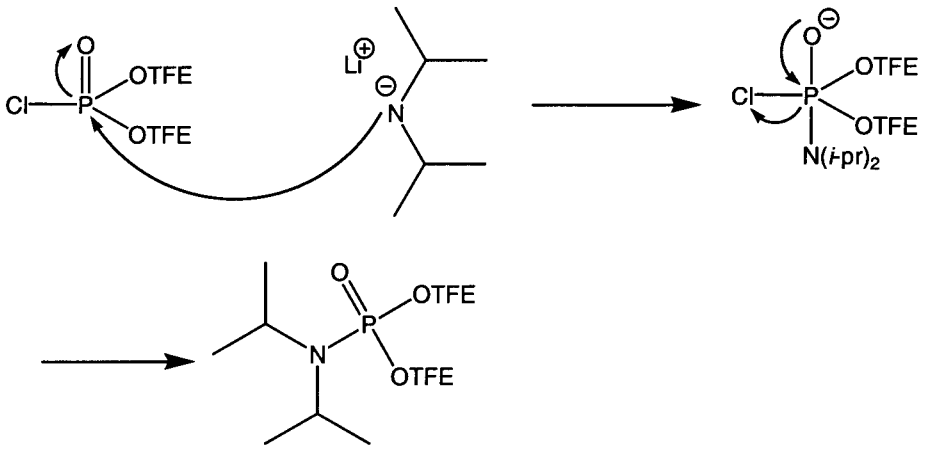


Figure 27

increase in yields for all three ketones. By warming to room temperature, the rate of the

deprotonation reaction was accelerated by a factor of 20 (a popular chemical approximation is that for every 10 degree increase in temperature, the reaction rate increases by a factor of two), thus ensuring LDA was acting on the ketone and not on the phosphorochloridate. Indeed, formation of phosphoramide byproduct dropped dramatically; from as high as 60% (GC) to as low as 7%. Chromatographic conditions were also changed, with an 80% hexane/20% diethyl ether being the most effective elution solvent. It should be noted that when the temperature profile changes were enacted, addition of co-solvents or solvent changes did not appreciably effect yield. ^{13}C spectra of the three ketone products **2**, **3**, and **4** all display the characteristic pair of doublets of quartets, indicating the bis(trifluoroethyl) phosphate moiety had been incorporated into all three ketone enolates. Maximum isolated yields are 77% for **2**, 80% for **3**, and 65% for **4**. These yields easily surpass those reported by Stock[32] and Oyeamalu.[36] In addition to these three ketones, the derivatization of phenol to the arylphosphate was also undertaken.

Due to the fact that phenol has no electrophilic center, it was not necessary to use LDA as a base because the nucleophilicity of *n*-butyllithium was not a concern. Therefore the formation of **6** was conducted in THF at –78 °C using *n*-butyllithium as the base. The reaction mixture containing the phenolate anion was allowed to warm to room temperature to ensure complete deprotonation of the phenolic proton (pka ~ 20) by the base. The reaction mixture was then recooled to –78°C, and neat phosphorochloridate was added. Flash column chromatography (9:1, hexane/ethyl acetate) yielded **6** in 67% yield. Modifications similar to those attempted in ketone derivitizations (co-solvents and solvents) were attempted, as were different bases (sodium hydride and LDA). Optimum

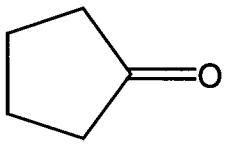
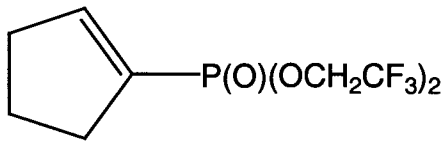
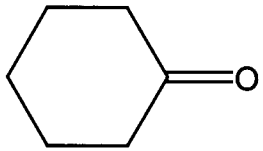
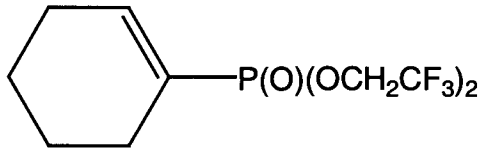
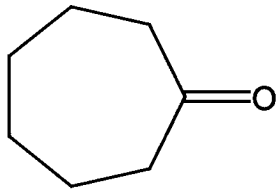
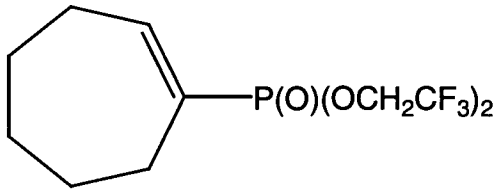
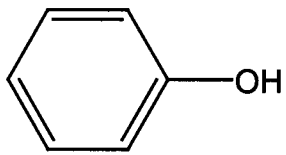
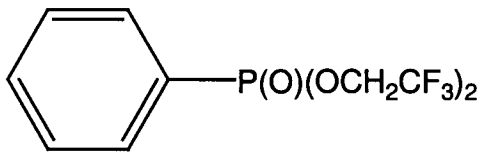
Starting Material	Phosphorylated Product	Entry	Yield
		2	77%
		3	80%
		4	65%
		6	73%

Table 3: Vinyl- and Aryl Phosphate Yields

yields were recorded when the reaction was performed entirely at room temperature. No co-solvents were utilized, the reaction was performed in THF, and **6** was isolated after column chromatography (4:1, hexane/diethyl ether) in 73% yield.

2.1. 3: Attempted Stille Couplings

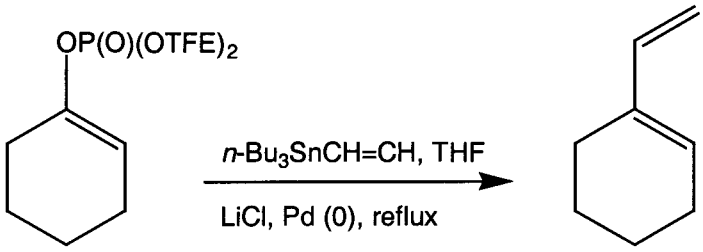


Figure 28

Once vinylphosphate starting materials were synthesized, their effectiveness in the Stille coupling (**Figure 28**) was examined. The general procedure is as follows: to a solution of vinylphosphate (**2**, **3**, **4**, **6**) (0.5 mmol) in THF (10 mL) was added tri-*n*-butyl(vinyl)tin (1 mmol, 0.317 g) and lithium chloride (3.0 mmol, 0.122 g). The reaction flask was then degassed with argon, and catalyst (0.05 mmol) in 10 mL THF was added. The reaction mixture was then refluxed for two hours.

Initial investigations on the coupling of vinyl- and arylphosphates with tri-*n*-butyl(vinyl)tin proved unsuccessful. No coupling turnover was recorded under the general reaction conditions shown above. NMR data indicated substantial amounts of tri-*n*-butyl(vinyl)tin still present, and column chromatography (10:1 hexane:ethyl acetate) yielded tri-*n*-butyl(vinyl)tin in varying recovery percentages. In addition to THF, dioxane, glyme, and hexane were investigated as solvents with varying reactant concentrations to no avail.

Stille has shown[14] that lithium chloride is necessary to allow the catalytic cycle to proceed. The first step, oxidative addition of the vinylphosphate to palladium, remains

unchanged with the addition of two trifluoroethyl groups to the phosphate. The phosphate is not removed by transmetalation though, as the catalytic cycle would suggest. The removal of the electrophile is accomplished by chloride ion, which then is exchanged for the vinyl group through transmetalation. Once the spontaneous reductive elimination of the product has occurred, the catalyst is able to reenter the catalytic cycle. The failure of bis(trifluoroethyl) vinylphosphates to couple successfully through this mechanism indicates failure in one (or more) step(s) of the catalytic cycle. The catalyst used in this work, tetrakis(triphenylphosphine) palladium(0), eliminates two triphenylphosphine groups either in tandem with or immediately preceding the oxidative addition, and this step is traceable and verifiable by ^{31}P NMR. Indeed, in concert with appearance of the triphenylphosphine peak (^{31}P δ -5.45 ppm) is the disappearance of the vinylphosphate peak (~ -6.4 ppm) indicating that oxidative addition to the catalyst had occurred.

GC/MS data indicated that tri-*n*-butyltin chloride was also formed if the reaction was allowed to proceed for longer periods of time (72 + hours). This indicates that the catalytic cycle reached transmetalation, albeit very slowly and in very low percentage, but would go no farther. Shorter reaction times simply resulted in the isolation of starting materials. Experimental evidence, then, indicates the coupling was occurring, but the catalytic cycle was shutting down before transmetalation. Since transmetalation is typically the rate-determining step, and it was occurring very slowly, the reaction itself had an extremely small k_{cat}. It would appear that instead of the enhanced electrophilicity having a positive effect on the coupling reaction, its effect was instead negative.

The electrophile itself is adding to the catalyst surface (this was verified by stoichiometric addition) but is not able to be removed by transmetalation due to the

strength of the phosphorus-to catalyst-bond, and the catalytic cycle is shutting down at that point. The Stille coupling of vinyl- or arylbis(trifluoroethyl) phosphates under catalysis by tetrakis(triphenylphosphine) palladium (0) or dichlorobis (triphenylphosphine) palladium (II) is ineffective as a means of generating conjugated dienes. Future work should include the use of different palladium catalysts; that is, the catalyst should incorporate ligands that are more electron-donating, such that the transmetalation and reductive elimination steps of the catalytic cycle (on which the coupling is predicated) will be more favorable, and thus more apt to occur. The effects of other solvents, such as dimethylformamide (which has been shown to be an effective solvent for coupling reactions), should also be investigated.

Part 2: Cyclic Ketene Acetal Phosphates as Electrophiles in the Stille Coupling

In lieu of the failure of ketone-derived vinylphosphates to successfully navigate the Stille coupling and the success shown[21] by Nicolaou of lactone-derived cyclic ketene acetal phosphates to do so, the next aspect was to determine if similar systems containing the bis(trifluoroethyl)phosphate moiety would succeed where the ketones had failed. Nicolaou had shown that tetrakis(triphenylphosphine) palladium (0) would successfully catalyze a Stille coupling between a cyclic ketene acetal phosphate (lactone vinyl phosphate) and tri-*n*-butyl(vinyl) tin. The presence of the ring oxygen would, however, present additional synthetic difficulties as the lithium counter-ion could be coordinated between the ring oxygen and the enolate oxygen, thereby reducing the ability of the enolate oxygen to initiate the $S^NP(V)$ reaction with bis(2,2,2-trifluoroethyl) phosphorochloridate, by decreasing the nucleophilicity of the oxygen through the formation of the aforementioned coordination complex. To combat this, methodology

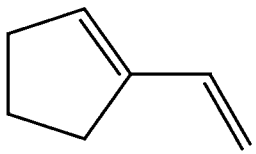
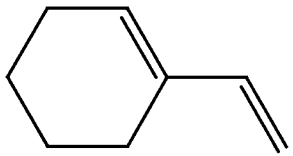
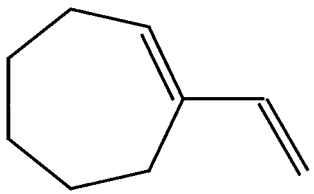
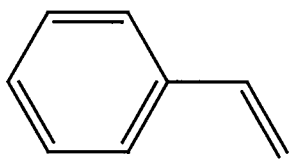
Starting Material	Coupling Product	Coupling Type	Entry	Yield
2		Stille	15	0%
3		Stille	16	0%
4		Stille	17	0%
6		Stille, Suzuki	18	0%

Table 4: Vinyl Phosphate Coupling Yields

similar to that used to generate vinylphosphates from ketones would be used, with the addition of a co-solvent capable of coordinating the lithium counter-ion Hexamethylphosphoramide (HMPA) and 12-crown-4 were used as coordinating agents in the phosphorylation of δ-valerolactone, ε-caprolactone, and γ-butyrolactone.

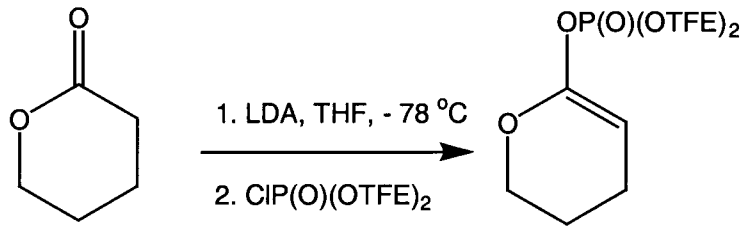


Figure 29

2.2.1: Synthesis of cyclic ketene acetal phosphates **7**, **8**, and **9**

In order to investigate the ability of bis(fluoroalkyl)-containing cyclic ketene acetal phosphates to successfully navigate the Stille coupling (**Figure 29**) these compounds had to first be synthesized. Also necessary was a methodological treatment of the optimal way to treat the lithium counter-ion. The general procedure is as follows: to a solution of LDA prepared *in situ* from diisopropylamine (0.77 mL, 5.5 mmol) and n-butyllithium (3.75 mL of a 1.6 M solution in hexane, 5.5 mmol) in 25 mL THF at –78 °C was added lactone (5 mmol) dropwise. This solution was allowed to warm to room temperature, and was then recooled to –78 ° C. HMPA (0.87 mL, 5 mmol) was added, and the reaction mixture was allowed to stir for 30 minutes. Bis(2,2,2-trifluoroethyl) phosphorochloridate (0.97 mL, 6 mmol) was then added dropwise, and the mixture was allowed to warm to room temperature over 24 hours. ^{31}P NMR indicated substantial formation of cyclic ketene acetal phosphates **7**, **8**, and **9**, but flash column chromatography in various solvent systems failed to produce **7**, **8**, or **9**. Small ring ketene

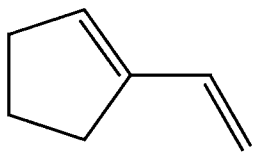
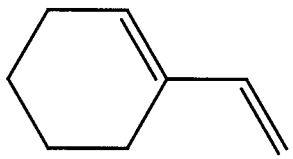
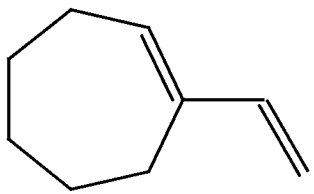
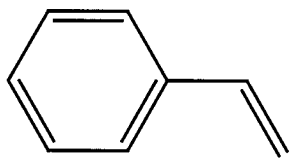
Starting Material	Coupling Product	Coupling Type	Entry	Yield
2		Stille	15	0%
3		Stille	16	0%
4		Stille	17	0%
6		Stille, Suzuki	18	0%

Table 4: Vinyl Phosphate Coupling Yields

similar to that used to generate vinylphosphates from ketones would be used, with the addition of a co-solvent capable of coordinating the lithium counter-ion Hexamethylphosphoramide (HMPA) and 12-crown-4 were used as coordinating agents in the phosphorylation of δ-valerolactone, ε-caprolactone, and γ-butyrolactone.

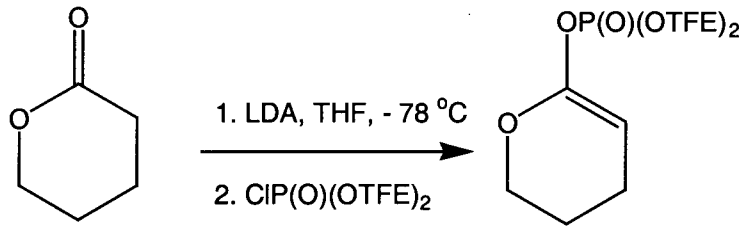


Figure 29

2.2.1: Synthesis of cyclic ketene acetal phosphates **7**, **8**, and **9**

In order to investigate the ability of bis(fluoroalkyl)-containing cyclic ketene acetal phosphates to successfully navigate the Stille coupling (**Figure 29**) these compounds had to first be synthesized. Also necessary was a methodological treatment of the optimal way to treat the lithium counter-ion. The general procedure is as follows: to a solution of LDA prepared *in situ* from diisopropylamine (0.77 mL, 5.5 mmol) and n-butyllithium (3.75 mL of a 1.6 M solution in hexane, 5.5 mmol) in 25 mL THF at –78 °C was added lactone (5 mmol) dropwise. This solution was allowed to warm to room temperature, and was then recooled to –78 ° C. HMPA (0.87 mL, 5 mmol) was added, and the reaction mixture was allowed to stir for 30 minutes. Bis(2,2,2-trifluoroethyl) phosphorochloridate (0.97 mL, 6 mmol) was then added dropwise, and the mixture was allowed to warm to room temperature over 24 hours. ^{31}P NMR indicated substantial formation of cyclic ketene acetal phosphates **7**, **8**, and **9**, but flash column chromatography in various solvent systems failed to produce **7**, **8**, or **9**. Small ring ketene

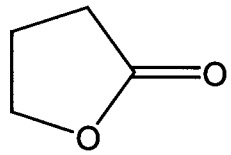
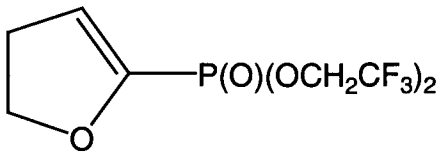
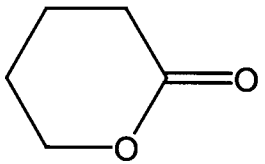
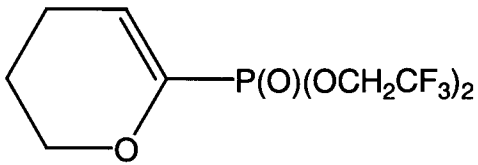
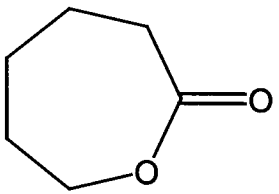
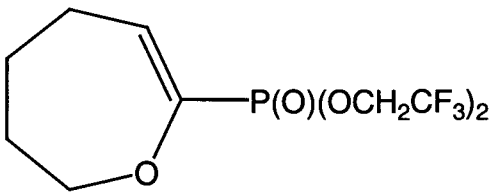
Starting Material	Phosphorylated Product	Entry	Yield
		7	0%
		8	0%
		9	0%

Table 5: Cyclic Ketene Acetal Phosphate Yields

acetal bis(trifluoroethyl) phosphates are unstable to flash column chromatography, and indeed are unstable to ambient conditions also. When samples of **7**, **8**, or **9** were left in atmosphere at ambient temperature, no ketene acetal bis(trifluoroethyl) phosphate was present by ^{31}P NMR after 24 hours, and the samples themselves turned into a black, tar-like compound. The on-column decomposition was believed to be due to the acidic silica surface catalyzing a rapid dephosphorylation of the ketene acetal bis(trifluoroethyl) phosphates. To ameliorate the acidity of the silica surface, flash column chromatography was performed on silica treated with 5% triethylamine in 80% hexane/20% diethyl ether. Despite the use of treated silica, flash column chromatography repeatedly failed to yield pure **7**, **8**, or **9**. It is noteworthy that the analogous diphenyl lactone vinyl phosphates were synthesized in good yield and did not possess the decomposition problems associated with the bis(trifluoroethyl) lactone vinyl phosphates.

2.2.2 Attempted Couplings of cyclic ketene acetal phosphates; Synthesis of **19a**, **19b**, **20a**, **20b**, **21a**, and **21b**

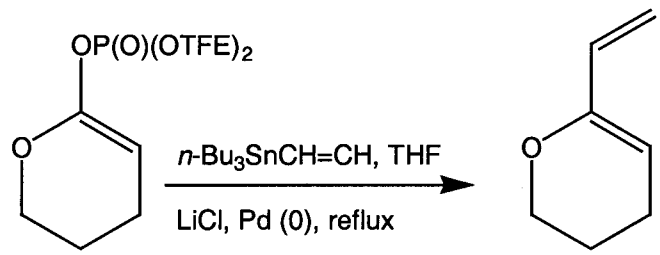


Figure 30

Since purified ketene acetal bis(trifluoroethyl) phosphates were not available, Stille couplings were attempted on crude reaction mixtures according to the general procedure (**Figure 30**). It is important to note that these crude reaction mixtures

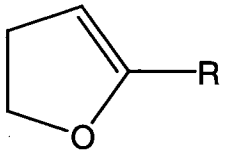
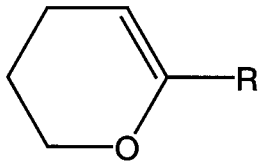
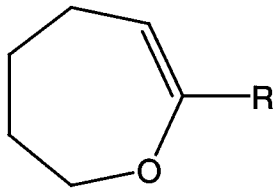
Starting Material	Coupling Product	Coupling Type	Entry	Yield	Notes
7		Stille, Suzuki	19a, 19b	0%	a, R = vinyl b, R = aryl
8		Stille, Suzuki	20a, 20b	0%	a, R = vinyl b, R = aryl
9		Stille, Suzuki	21a, 21b	0%	a, R = vinyl b, R = aryl

Table 6: Lactone Vinyl Phosphate Coupling Yields

contained substantial ketene acetal phosphate as determined by gas chromatography and ^{31}P NMR. Again, the bis(trifluoroethyl) group-containing phosphate failed to generate coupling turnover in the Stille coupling. The same crude reaction mixtures were also subjected to Suzuki conditions (see below) without success. The effects of increasing ring size and number of ring substituents on the stability of the cyclic ketene acetal phosphates should be investigated, and if pure product can be isolated, their coupling efficiency should also be investigated.

Part 3: The Suzuki Coupling

Concurrent with the conclusion that ketene acetal bis(trifluoroethyl) phosphates and bis(trifluoroethyl)vinyl phosphates would not couple to vinylstannanes to generate dienes via the Stille coupling was the discovery that these bis(trifluoroethyl)vinyl phosphates could be coupled to phenylboronic acid via the Suzuki coupling,[36] thereby succeeding where the Stille coupling had failed. This discovery was enough to prompt the final phase of this project, the use of bis(trifluoroethyl) dienylphosphates as electrophiles in the Suzuki coupling. The first step was to optimize the synthesis of several dienylphosphates from their parent enones.

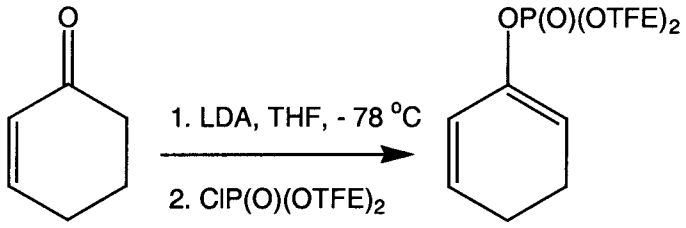
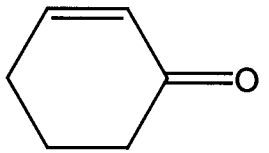
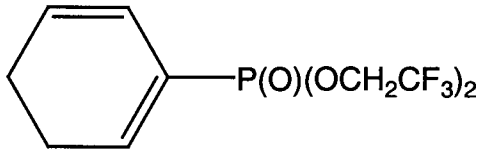
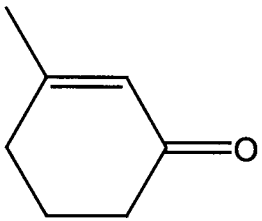
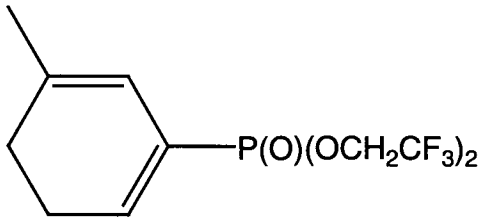
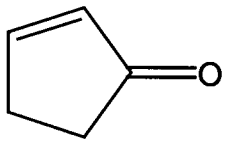
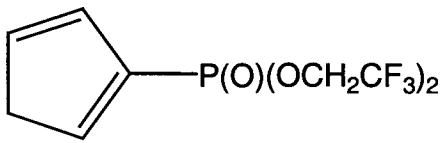
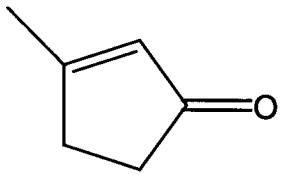
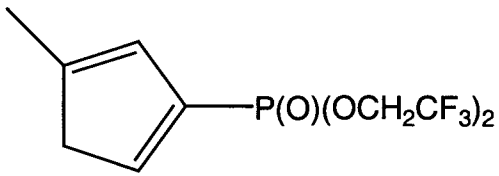
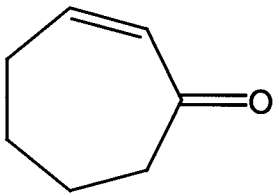
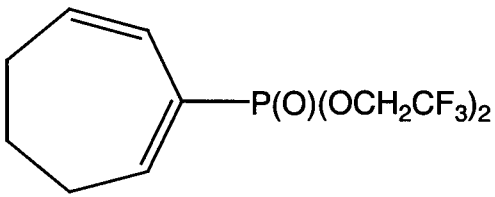


Figure 31

2.3.1: Synthesis of Dienyl Phosphates, **10**, **11**, **12**, **13**, **14**

Starting Material	Phosphorylated Product	Entry	Yield
		10	83%
		11	84%
		12	70%*
		13	72%*
		14	67%*

* by GC

Table 7: Dienyl Phosphate Yields

The synthesis of dienyl phosphates **10-14** (**Figure 31**) closely mirrored that of the synthesis of the previous vinyl phosphates. The general procedure is as follows: to a solution of LDA (5.5 mmol) at –78 °C prepared *in situ* from diisopropylamine and *n*-butyllithium in 25 mL THF was added enone (5 mmol) dropwise. Once the addition was complete, the reaction mixture was allowed to warm to room temperature (25 °C) to ensure complete deprotonation of the enone. The reaction mixture was then recooled to –78 °C, at which time bis(2,2,2-trifluoroethyl)phosphorochloridate (6 mmol, 0.97 mL) was added in a dropwise manner. The reaction mixture was then allowed to warm to room temperature over a period of 18 hours. The dienyl phosphate products were obtained as colorless to light yellow oils after flash column chromatography (4:1 hexanes/diethyl ether).

Initial investigation of the ability to generate dienyl phosphates from a method identical to that used for the generation of vinyl phosphates showed that this method was effective, however the full 24 hour reaction time was not necessary, and a full 6 hours could be subtracted from the reaction time without detriment. It was also shown that allowing the reaction mixture to stir for an additional 6 hours (i.e. a full 24 hours) did not generate appreciable amounts of byproduct and did not hamper the reaction in any way. It appears that the earlier methodological work that was done to optimize yield of vinyl phosphates from ketones was carried forth directly into the derivatization of enones. Addition of lithium-coordinating co-solvents did not appreciably affect yield.

2.3.2: Dienylphosphates in the Suzuki coupling; Synthesis of **22**, **23**, **24**, **25**, **26**

Once dienyl phosphate products were generated, their effectiveness as organic

electrophiles in the Suzuki coupling (**Figure 32**) was examined. In lieu of the inability of tetrakis(triphenylphosphine)palladium (0) to catalyze any coupling reaction involving the

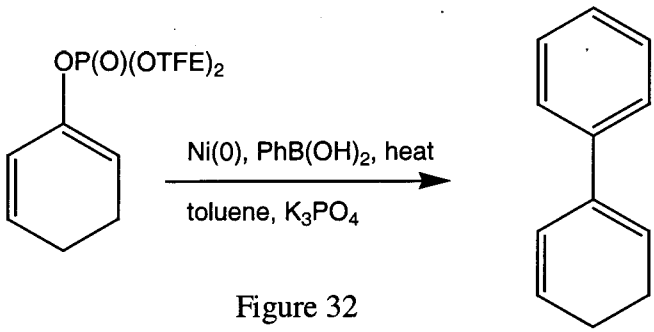
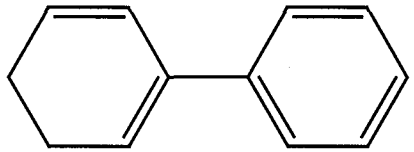
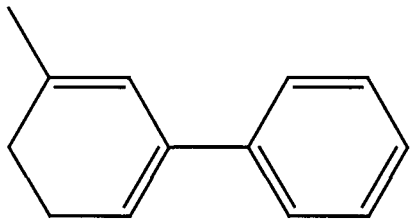
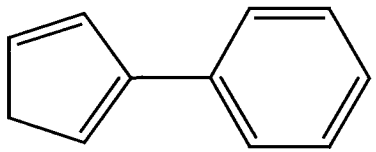
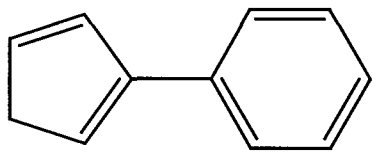
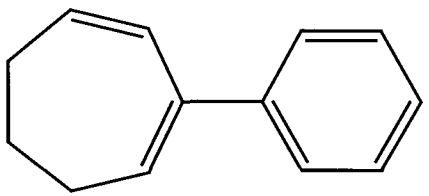


Figure 32

bis(2,2,2-trifluoroethyl) phosphate moiety, palladium was abandoned as a catalyst. Suzuki couplings had been shown to be successful[19] on analogous systems using nickel (0) as the catalytic species, and thus Ni (0) was selected as the most logical successor to palladium as the catalyst of interest. The general procedure is as follows: to a solution of [1, 1'-bis(diphenylphosphino)ferrocene]dichloronickel (II) (0.0213 g, 0.03 mmol) in 8 mL anhydrous toluene under argon was added *n*-butyllithium (0.188 mL, 0.3 mmol) in a dropwise manner. Once the addition was completed, the reaction mixture was allowed to stir for 30 minutes at 25 °C. To a pressure tube which was degassed with argon and sealed with a septum was added dienyl phosphate (2.5 mmol), 1, 1'-bis-(diphenylphosphino)ferrocene (0.045 g, 0.08 mmol), potassium phosphate (tribasic, anhydrous) (1.06 g, 5 mmol), phenylboronic acid (0.710 g, 5 mmol) and toluene (2 mL). This mixture was also allowed to stir for 30 minutes under positive pressure of argon. The catalyst solution was then cannulated into the pressure tube, which was then degassed for an additional 10 minutes and sealed. This mixture was then stirred in an oil bath at 90 °C for 72 hours. The crude reaction mixture was solvated with diethyl ether

Starting Material	Coupling Product	Coupling Type	Entry	Yield	Notes
10		Suzuki	22	38%	1
11		Suzuki	23	44%	1
12		Suzuki	24	0%	2
13		Suzuki	25	0%	2
14		Suzuki	26	0%	2

1 = Crude Yield
2 = Did not attempt

Table 8: Dienyl Phosphate Coupling Yields

(10 mL) and then extracted with water (2 x 5 mL) and brine (2 x 5 mL), and dried over magnesium sulfate. The solvent was removed by rotary evaporation and the product was purified by flash column chromatography (10:1 hexane/ethyl acetate) to generate pure product **22-26** as colorless oils in varying yields.

In lieu of the long reaction time necessary for the above reactions, the addition of zinc as a co-catalyst was also investigated. Oyeamalu[36] had previously shown that the above procedure with the addition of an equivalent of zinc would successfully generate coupling product from a vinyl phosphate and phenylboronic acid in 24 to 48 hours. This procedure was also applicable to dienyl phosphates. The general procedure is as follows: to a solution of [1, 1'-Bis(diphenylphosphino)ferrocene]dichloronickel (II) (0.0213 g, 0.03 mmol) in 8 mL anhydrous toluene under argon was added *n*-butyllithium (0.188 mL, 0.3 mmol) in a dropwise manner. Once the addition was completed, the reaction mixture was allowed to stir for 30 minutes at 25 °C. To a pressure tube which was degassed with argon and sealed with a septum was added dienylphosphate (2.5 mmol), 1, 1'-Bis(diphenylphosphino)ferrocene (0.045 g, 0.08 mmol), potassium phosphate (tribasic, anhydrous) (1.06 g, 5 mmol), phenylboronic acid (0.710 g, 5 mmol), zinc (0.16 g, 2.5 mmol), and anhydrous toluene (2 mL). This mixture was also allowed to stir for 30 minutes under positive pressure of argon. The catalyst solution was then cannulated into the pressure tube, which was then degassed for an additional 10 minutes and sealed. This mixture was then stirred in an oil bath at 90 °C for 24 hours. The crude reaction mixture was solvated with diethyl ether (10 mL) and then extracted with water (2 x 5 mL) and brine (2 x 5 mL), and dried over magnesium sulfate. Flash column chromatography (10:1

hexane/ethyl acetate) generated pure coupling products as colorless oils in varying percent yields.

The apparent co-catalysis of this coupling reaction by zinc indicates that this is not a true catalytic event; the theoretical catalytic cycle does not appear to be operating here. Rather, this appears to be a single-electron transfer event, such that the addition of zinc speeds the reaction up. Zinc appears to be acting as the chain-carrier in the radical-type coupling operating here. Future work should include the addition of a common radical scavenger, such as butylated hydroxytoluene (BHT), to the pressure tube and the examination of its effects, that is, if the addition of BHT shuts the reaction down completely that would indicate that the reaction is happening via a process that would be hindered by the presence of BHT, namely a single-electron transfer.

Part 4: Spectral Interpretations

All compounds whose syntheses are reported were characterized by ^{1}H, ^{13}C, and ^{31}P (where applicable) NMR. All relevant spectra can be seen in the appendix at the end of this document.

2.4.1 bis(2,2,2-trifluoroethyl)phosphorochloridate, **1**

Since ^{13}C, ^{31}P, and ^{19}F are all spin ½ nuclei, coupling between these atoms is allowed as well as anticipated. The ^{13}C spectrum of **1** (**Figure 33**) shows the characteristic set of doublets of quartets (dq) that are expected. As expected, the first doublet of quartets is seen at 64.0 ppm, and corresponds to the methylene carbons, as shown below. The second doublet of quartets is seen as 117.5 ppm, and corresponds to the fluorine-bearing carbons. The multiplicity results from carbon coupling to three fluorine molecules, thereby generating the quartet, in conjunction with the fact that the

two carbon signals are also split by phosphorous into doublets. Due to their proximity to three highly electronegative fluorine atoms, the fluorine-bearing carbons have C-F coupling constants

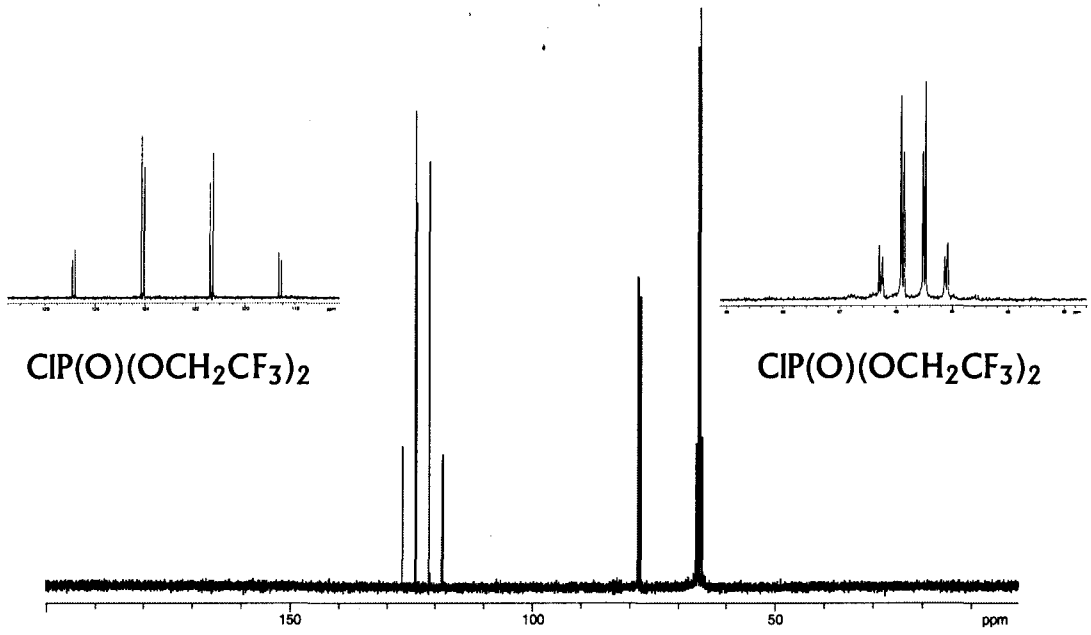


Figure 33

that are much larger than the C-F coupling constants shown by the methylene carbons (276.7 Hz vs. 38.8 Hz) and the signal itself is shifted much farther downfield. Carbon-phosphorous coupling constants are relatively similar at 11.3 Hz for the fluorine-bearing carbons and 5.4 Hz for the methylene carbons. The triplet at 77.0 ppm is resultant from the carbon in the solvent, deuterated chloroform, ($CDCl_3$) coupling to deuterium ($I = 1$). These carbon peaks are very distinctive and will be used as indicators that the desired compounds incorporating the bis(2,2,2,-trifluoroethyl) phosphate moiety were synthesized. The $CDCl_3$ triplet at 77.0 ppm is a reference peak and will be present in

every carbon spectrum, and will therefore be disregarded for the rest of this manuscript. The ^{31}P spectrum shows one peak, as expected, at 6.0 ppm (relative to phosphoric acid, δ = 0.0 ppm). The presence of one peak by ^{31}P indicates the presence of one type of phosphorous environment in the sample, which can be loosely translated into the presence of one type of phosphorous-containing compound. This facet of ^{31}P NMR proved to be a useful tool in determining the purity of both crude and purified reaction mixtures. The ^{1}H spectrum shows a multiplet at δ 4.41 ppm, which is actually a set of overlapping doublets of quartets corresponding to the methylene protons in the molecule. Since the H-F and H-P coupling constants are similar, the signals themselves overlap and produce the multiplet shown (J = 8.1 Hz) instead of two distinct dq's. This signal will also be used in all subsequent spectra to verify the presence of this type of methylene proton, thereby verifying that the bis(2,2,2-trifluoroethyl) phosphate was inserted into the compound as desired.

2.4.2 Vinyl Phosphates **2**, **3**, **4**, and **6**

The most empirically useful spectrum for these vinyl phosphates is the ^{31}P NMR spectrum. Noteworthy is the presence of one peak, δ -6.4 ppm. It was also determined empirically that five- and six-membered rings containing the bis(2,2,2-trifluoroethyl) phosphate moiety have chemical shifts that are –6.4 +/- 0.5 ppm. This seems intuitive due to the fact that the addition of one carbon does not affect the phosphorous environment appreciably. This is another aspect of the ^{31}P NMR spectra that proved to be extremely useful, that is, the chemical shifts were repeatable and consistent. The ^{1}H spectrum includes the expected multiplet resulting from the methylene protons in the bis(2,2,2-trifluoroethyl) phosphate, as discussed earlier. In addition, also present should

be signals corresponding to the vinylic proton (5 – 6 ppm), the sets of allylic protons(2 – 3 ppm), and the set(s) of homoallylic protons (1 – ppm). Most important is the appearance of the peak corresponding to the vinylic proton between 5 and 6 ppm, with the exception of **6**, which does not contain any vinylic protons. In all cases the recorded spectra display the expected peaks.

2.4.3 Cyclic Ketene Acetal Phosphates 7, 8, and 9

^{31}P NMR of the crude reaction mixtures of **7**, **8**, and **9** indicates substantial formation of the requisite lactone vinyl phosphates but, as discussed earlier, no purified compounds were obtained. Therefore, no spectra were recorded for these compounds.

2.4.4 Dienyl Phosphates 10, 11, 12, 13, and 14

Formation of the dienyl phosphates could be characterized by the presence of two vinylic peaks in the ^{1}H NMR spectrum for **11** and **13** and three vinylic peaks for **10**, **12**, and **14**. These peaks are between 5 and 6 ppm, which is the typical range for vinylic protons. These compounds also show consistent ^{31}P NMR spectra, that is, one peak by

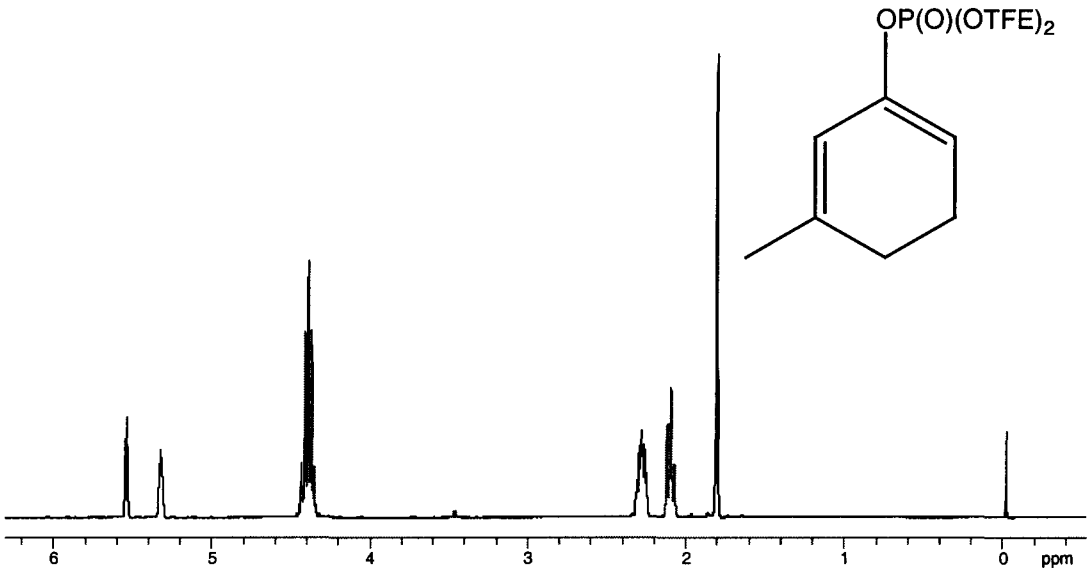


Figure 34

^{31}P at $\delta \approx -6.4$ ppm. **Figure 34** shows a typical ^{1}H NMR spectrum of a dienyl phosphate, **11** in this case. The two multiplets at 5.3 ppm and 5.5 ppm are the two vinylic protons in the molecule. These signals should be seen as doublets of doublets of doublets, due to coupling to phosphorus and the adjacent non-equivalent protons, but they appear here as multiplets. The multiplet at δ 4.4 ppm is the signal corresponding to the methylene protons in the trifluoroethyl groups, as discussed earlier. The multiplets at 2.1 ppm and 2.3 ppm result from the two sets of allylic protons, and the strong singlet at 1.6 ppm is due to the allylic methyl group at C5.

2.4.5 Coupling Products (**15-26**)

As discussed earlier, products **15** through **21a** and **21b** were unable to be generated. Therefore, no spectra were recorded for these compounds. The spectra for

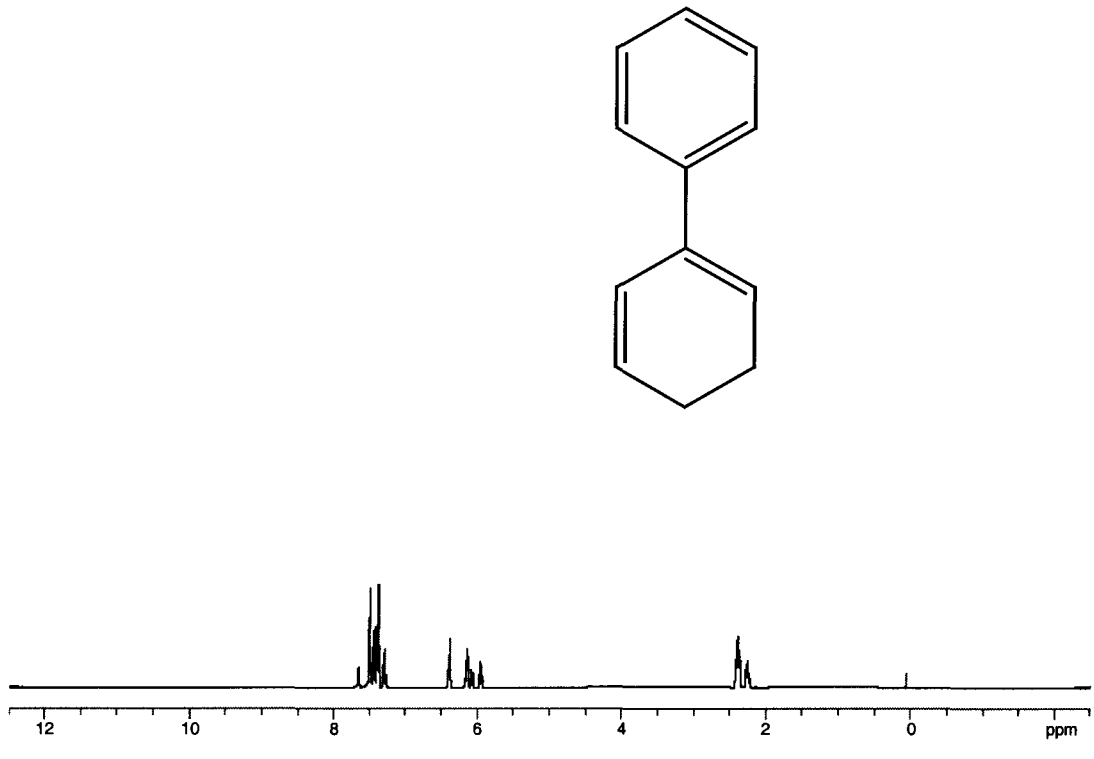


Figure 35

coupling products **22** through **26** display the desired peaks. Most noteworthy, again, is the presence of the correct number of vinylic peaks. This, combined with the presence of the correct number of allylic, homoallylic, and aromatic peaks indicates that the coupling products shown were generated successfully. As an example, **Figure 35** shows the ^{1}H spectrum from **22**, which displays signals corresponding to the aromatic protons (δ 7.1-7.3 ppm), the three vinylic protons in the molecule (δ 5.9, 6.1, and 6.3), and the two sets of allylic protons at δ 2.4 and 2.6 ppm. This data reaffirms the fact that the desired product was formed.

Part 5: Conclusions

As with any good research project, this project provided answers as well as questions. It appears that Stock was correct in his assertion[32] that the methodology used to generate the bis(2,2,2-trifluoroethyl) vinyl phosphates, especially those arising from cyclopentanone and cyclohexanone, was not quite optimized. It is believed that this methodology is now optimized, and yields above 70% and even 80% are now commonplace. These same vinyl phosphates, however, do not appear to be useful electrophiles for the Stille coupling when palladium is used as a catalyst. As stated previously, the effects of more electron-donating ligands on palladium might provide the activation energy necessary for the transmetalation and reductive elimination steps of the catalytic cycle to occur. The destabilization of lactone vinyl phosphates by the highly electronegative trifluoroethoxy groups present and whether using rings that are more highly functionalized would ameliorate this should be addressed also, as it was concluded that these compounds were extremely unstable. Lastly, it was concluded that enones could be converted to their corresponding dienyl phosphates by methodology similar to

that used to generate the aforementioned vinyl phosphates, and that these dienyl phosphates could be passed through a nickel (0) mediated variant of the Suzuki coupling, albeit in moderate yields. It is believed that this Suzuki method is not yet optimized, and further work could generate better coupling turnover.

Chapter 3: Experimental

Part 1: General Methods

Diisopropylamine and pentane were distilled from calcium hydride prior to use. THF and dioxane were distilled from sodium/benzophenone prior to use. All commercial reagents were purchased from Aldrich and were used without further purification. All air-sensitive reactions were performed under positive pressure of argon. Flash column chromatography was conducted with Merck grade 9385, 230-400 mesh silica. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 250 μm silica plates. TLC plates were visualized with ultraviolet light and stained with phosphomolybdic acid (PMA) in ethanol followed by heating. Gas Chromatography was performed on a Hewlett-Packard 5890 Series II Gas Chromatograph equipped with a flame-ionization detector. NMR spectra (^{1}H, ^{13}C, and ^{31}P) were recorded on a Varian Gemini 2000, 400 MHz spectrometer with $CDCl_3$ as the solvent. The ^{1}H chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). The ^{13}C chemical shifts are reported in ppm downfield from TMS with $CDCl_3$ (77.0 ppm) as the internal standard. ^{31}P chemical shifts are reported in ppm down- or upfield from phosphoric acid (external standard). Coupling constants are reported in Hertz (Hz).

Part 2: Experimental Methods

3.2.1 Bis(2,2,2-trifluoroethyl) phosphorochloridate (**1**)[33]

To a solution of bis(2,2,2-trifluoroethyl) phosphite (50 g, 203 mmol) in benzene (55 mL) at 0 °C was added dropwise a solution of sulfuryl chloride (20.25 mL, 203 mmol) in benzene (55 mL). Once the addition was complete, the reaction mixture was allowed to warm to room temperature over a period of 24 hours. The benzene was then removed by

rotary evaporation, and high vacuum distillation yielded pure product **1** (50.0 g, 88%) as a colorless oil.

^{1}H NMR δ 4.41-4.54 (4H, m)

^{13}C NMR δ 117.5 (2, dq, J = 276.7, 11.3 Hz), 64.6 (2, dq, J = 38.8, 5.4 Hz)

^{31}P NMR δ 5.977

3.2.2 **1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]cyclopentene (2).**

3.2.2a Method 1, General Procedure for the Preparation of bis(2,2,2-trifluoroethyl) Vinyl Phosphates.

To a solution of LDA [5.5 mmol, prepared *in situ* from diisopropylamine (0.77 mL) and *n*-butyllithium (3.75 mL of a 1.6 M solution in hexane in anhydrous tetrahydrofuran (25 mL) at –78 °C was added dropwise *via* syringe neat cyclopentanone (0.45 mL, 5 mmol). Once the addition was complete, the reaction mixture was allowed to warm to 0 °C for 10 minutes and then to 25 °C for 20 minutes, then was recooled to - 78 °C. Once the reaction mixture reached –78 °C, neat bis(2,2,2-trifluoroethyl) phosphorochloridate (0.95 mL, 5.5 mmol) was added dropwise *via* syringe. The reaction mixture was allowed to warm gradually to 25 °C over a period of 24 hours. The crude mixture was then diluted with diethyl ether (10 mL), and extracted with saturated ammonium chloride (NH_4Cl, 3 x 10 mL), deionized water (2 x 10 mL), and brine (2 x 10 mL). The aqueous layers were combined (with the exception of the brine washes) and back extracted with diethyl ether (2 x 10 mL), and the organic layers were combined and dried over anhydrous magnesium sulfate ($MgSO_4$). The solvent was removed *en vacuo*, and flash column chromatography (80% hexanes, 20% diethyl ether) produced **2** (1.26 g, 77%) as a colorless oil.

^{1}H NMR δ 5.33-5.28 (1H, m), 4.44-4.33 (4H, m), 2.48-2.40 (2H, m), 2.36-2.28 (2H, m), 1.98-1.89 (2H, m).

^{13}C NMR δ 148.9 (d, J = 9.3 Hz), 122.0 (2, dq, J = 276.7, 11.3 Hz), 111.2 (d, J = 5.1 Hz), 64.2 (2, dq, J = 38.8, 5.4 Hz), 31.1 (d, J = 4.7 Hz), 28.3 (s), 20.9 (s).

^{31}P NMR δ - 6.95.

3.2.2b Method 2

To a solution of LDA (5.5 mmol) in THF generated in accordance with the general procedure was added neat cyclopentanone (0.45 mL, 5 mmol) dropwise *via* syringe. After the addition was complete, the reaction mixture was allowed to stir for 30 minutes. Neat bis(2,2,2-trifluoroethyl)phosphorochloridate (0.95 mL, 5.5 mmol) was then added dropwise, and the mixture was allowed to warm to room temperature over 24 hours. Standard workup and purification by column chromatography were performed according to the general procedure, yielding **2** (0.98 g, 60%) as a colorless, viscous oil.

3.2.2c Method 3

Cyclopentanone (0.45 mL, 5.0 mmol) in 15 mL THF was added via pressure-equalizing addition funnel to a solution of LDA (5.5 mmol) in THF (15 mL) at – 78 °C. The resulting enolate was then treated with bis(2,2,2-trifluoroethyl)phosphorochloridate (0.95 mL, 5.5 mmol) according to the general procedure. Standard workup and purification by column chromatography yielded **2** (0.66 g, 40%) as a colorless oil.

3.2.2d Method 4

After addition of cyclopentanone (0.45 mL, 5.0 mmol) to a solution of LDA in THF (5.5 mmol in 15 mL) at –78 °C, the resulting enolate was treated with bis(2,2,2-trifluoroethyl) phosphorochloridate in 15 mL THF, which was added dropwise through a pressure-

equalizing addition funnel. The resulting mixture was then allowed to stir and warm to room temperature over a period of 24 hours. The crude reaction mixture was then extracted and purified (by column chromatography) according to general procedure to yield the desired product (0.67 g, 41%).

3.2.2e Method 5

To a solution of LDA prepared in situ according to general procedure in 15 mL diethyl ether (anhydrous, distilled from CaH_2) was added cyclopentanone (0.45 mL, 5 mmol) dropwise via syringe. The mixture was allowed to stir for 30 minutes, and bis(2,2,2-trifluoroethyl)phosphorochloridate (0.95, 5.5 mmol) was added dropwise. The reaction mixture was quenched by the addition acetic acid (5 mL of a 1M solution in diethyl ether), filtered through a 1 cm layer of florisil, and then extracted and purified according to general procedure. 0.88 g (54%) of desired product was obtained as a light oil.

3.2.2f Method 6

To a solution of the enolate of cyclopentanone (0.45 mL, 5 mmol in THF), which was generated in accordance with the general procedure, was added hexamethylphosphoramide (0.87 mL, 1 eq.). After stirring for 30 minutes at – 78 °C, the enolate was treated with bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol). The mixture was then allowed to warm to room temperature over a period of 24 hours. The resulting crude product was purified by column chromatography after standard workup, and **2** was isolated (0.75 g, 46%) as a light oil.

3.2.2g Method 7

After addition of cyclopentanone (0.45 mL, 5 mmol) to a solution of LDA in THF (1.1 eq. in 25 mL), the resulting enolate was treated sequentially with 12-crown-4 (0.81 mL, 5

mmol), and bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol) according to general procedure. Final purification after standard workup yielded 0.69 g (42%) of **2** as a colorless oil.

3.2.3. **1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy] cyclohexene (3).**

3.2.3a Method 1

To a solution of LDA (1.1 eq.) in THF (25 mL) was added cyclohexanone (0.52 mL, 5 mmol) *via* syringe in accordance with the general procedure. Bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol) was then added to the resulting enolate. Standard workup and purification by column chromatography were performed in accordance with the general procedure, and generated **3** (1.37 g, 80%) as a light yellow oil.

^{1}H δ 5.5-5.45 (1H, m), 4.4-4.3 (4H, m), 2.15-2.10 (2H, m), 2.05-1.98 (2H, m), 1.70-1.63 (2H, m), 1.53-1.45 (2H, m).

^{13}C δ 147.15 (d, J = 9.6 Hz), 122.0 (2, dq, J = 276.7, 11.3 Hz), 112.27 (d, J = 5.3 Hz), 64.0 (2, dq, J = 38.8, 5.4 Hz), 23.47 (d, J = 3.1 Hz), 23.6 (s), 22.5 (s), 21.25 (s).

^{31}P δ - 6.69.

3.2.4 1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]cycloheptene (4)

3.2.4a Method 1

After addition of cycloheptanone (0.59 mL, 5 mmol) to a solution of LDA (5.5 mmol) prepared according to the general procedure, the resulting enolate was treated with bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol). The crude reaction mixture was then subjected to standard workup and purification conditions, yielding **4** (1.12 g, 65%) as a light oil.

^{1}H δ 5.69-5.64 (1H, m), 4.43-4.38 (4H, m), 2.42-2.37 (2H, m), 2.12-2.03 (2H, m), 1.72-1.56 (6H, m).

^{13}C δ 150.4 (d, *J* = 9.7 Hz), 122.0 (2, dq, *J* = 276.7, 11.3 Hz), 117.18 (d, *J* = 5.1 Hz), 64.1 (2, dq, *J* = 38.1, 5.4 Hz), 33.2 (d, *J* = 3.1 Hz), 30.5 (s), 27.0 (d, *J* = 1.4 Hz), 24.8, (s), 24.2 (s).

^{31}P δ - 6.70

3.2.5 **[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]benzene (6)**

3.2.5a Method 1

To a solution of phenol (0.47 g, 5 mmol, recrystallized from petroleum ether) in THF (25 mL) at 25 °C was added *n*-butyllithium (3.75 mL of a 1.6 M solution in hexane, 5.5 mmol) dropwise *via* syringe. The reaction mixture was allowed to stir for 30 minutes, and was subsequently treated with bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol). This mixture was allowed to stir for two hours. Standard workup and purification yielded **6** as a colorless oil (1.23 g, 73%).

^{1}H δ 7.4-7.18 (5H, m), 4.52-4.40 (4H, m).

^{13}C δ 149.4 (d, *J* = 6.9 Hz), 130.0 (s), 126.0 (s), 122.0 (2, dq, *J* = 276.7, 11.3 Hz), 119.8 (d, *J* = 5.2 Hz), 64.3 (2, dq, *J* = 38.1, 5.4 Hz).

^{31}P δ - 7.09.

3.2.5b Method 2

To a solution of phenol (0.47 g, 5 mmol) in THF (25 mL) at – 78 °C was added *n*-butyllithium (3.75 mL of a 1.6 M solution in hexane, 5.5 mmol). The reaction mixture was warmed to 0 °C, then subsequently recooled to – 78 °C and treated with HMPA (0.87 mL, 5 mmol) and allowed to stir for 30 minutes. Bis(2,2,2-trifluoroethyl)

phosphorochloridate (0.97 mL, 5.5 mmol) was then added, and the reaction was allowed to warm to room temperature over a period of 24 hours. Standard workup and chromatographic purification conditions produced the desired product (1.13 g, 67%).

3.2.5c Method 3

After addition of *n*-butyllithium (1.1 eq.) to a solution of phenol (0.47 g, 5 mmol) in 25 mL THF at – 78 °C, the resulting anion was treated sequentially with 12-crown-4 (1 eq.) and bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol). The reaction was then allowed to warm to 25 °C over 24 hours. After workup and purification by column chromatography according to the general procedure, **6** was obtained as a light oil (0.98 g, 58%).

3.2.5d Method 4

To a solution of sodium hydride (0.22 g of a 60% w/w dispersion in mineral oil, 5.5 mmol) in THF (15 mL) at 0 °C was added a solution of phenol (0.47 g, 5 mmol) in THF (10 mL) by pressure-equalizing addition funnel. After the addition was complete, the reaction was allowed to stir for 45 minutes and was subsequently treated with bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol). The reaction was allowed to warm to room temperature over 24 hours, and was worked up and purified according to the general procedure. Obtained as a colorless oil was **6** (0.57 g, 34%).

3.2.5e Method 5

To a solution of phenol (0.47 g, 5 mmol) in diethyl ether (25 mL, distilled off CaH_2) at 0 °C was added *n*-butyllithium (1.1 eq.). This reaction was allowed to stir for 30 minutes, and was treated with bis(2,2,2-trifluoroethyl)phosphorochloridate (1.1 eq.). The reaction

was then warmed to room temperature over 24 hours. Standard workup and chromatographic treatments produced 0.33 g (19%) of the desired product.

3.2.5 **2-vinyl-cyclopent-1-ene (15)**

3.2.5a Method 1, General Procedure for Attempted Stille Couplings of Vinyl Phosphates and Vinylstannanes

To tetrakis(triphenylphosphine) palladium (0) (0.05 eq.) was added THF (10 mL), and the solution was stirred under argon for 30 minutes. Lithium chloride (3.0 eq.) was then added, along with vinylphosphate (1 mmol), and tri-n-buty(vinyl)ltin(2.0 eq.). This solution was then refluxed for 2 hours under inert atmosphere. Standard workup and purification according to the general procedure yielded no trace of coupling product.

3.2.5b Method 2

To a solution of bis(triphenylphosphine)dichloropalladium (II) (0.01754 g, 0.025 mmol) in 10 mL THF was added vinylphosphate (0.5 mmol) and tri-*n*-butyl(vinyl)tin (0.3 mL, 0.5 mmol). This solution was refluxed for 2 hours and subsequently subjected to standard workup and chromatographic conditions. No coupling turnover was recorded.

3.2.5c Method 3

According to the general procedure, catalyst ($Pd(PPh_3)_4$, 0.05 mol %), vinyl phosphate (2.5 mmol), lithium chloride (3.0 eq.), and tri-*n*-butyl(vinyl)tin (1 eq.) were added to a flask. The flask was purged with argon, and 10 mL dioxane was added. This solution was then refluxed for 4 hours. Workup and purification yielded no coupling product.

3.2.5d Method 4

After addition of tri-*n*-butyl(vinyl)tin (1 eq.) to a flask containing vinyl phosphate (2.5 mmol), lithium chloride (.318 g, 2.5 mmol), tetrakis(triphenylphosphine)palladium (0)

(0.144 g, 2.5 mmol) and toluene (10 mL), the solution was refluxed under inert atmosphere for 24 hours. Standard workup and column chromatography according to the general procedure produced none of the desired product.

3.2.5e Method 5

All components were mixed according to the general procedure, and the mixture was refluxed for 48 hours. No turnover was recorded.

3.2.5f Method 6

The general procedure was followed exactly, with the exception of the reflux time being extended to 72 hours. None of the desired product was obtained.

3.2.5g Method 7

Method 4 was repeated exactly, with hexane as the solvent in place of dioxane. No desired product was obtained.

3.2.6 2-vinyl-cyclohex-1-ene (16)

3.2.6a Method 1

To a flask prepared according to the general procedure was added tetrakis (triphenylphosphine)palladium (0) (0.05 eq.) and THF (10 mL). This solution was stirred for 30 minutes under inert atmosphere. Lithium chloride (3.0 eq.) was then added, along with vinylphosphate (1 mmol), and tri-n-buty(vinyl)ltin(2.0 eq.). This solution was then refluxed for 2 hours under inert atmosphere. Standard workup and purification according to the general procedure yielded no trace of coupling product.

3.2.7 2-vinyl-cyclohept-1-ene (17)

3.2.7a Method 1

After addition of vinyl phosphate (1 mmol), lithium chloride (3.0 eq.), and tri-*n*-butyl(vinyl) tin (2.0 eq.) to a solution of tetrakis(triphenylphosphine) palladium (0) in THF (10 mL) under argon, the resulting solution was refluxed for two hours. Standard workup and purification yielded no desired product.

3.2.8 1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]-1,5-cyclohexadiene (10)

3.2.8a Method 1, General Procedure for the Synthesis of Dienyl bis(trifluoroethyl) Phosphates

To a solution of LDA (5.5 mmol, prepared *in situ* from diisopropylamine (0.77 mL) and *n*-butyllithium (3.75 mL of a 1.6 M solution in hexane) which had been generated at – 78 °C, warmed to room temperature, and then recooled to – 78 °C, was added 2-cyclohexen-1-one (0.48 mL, 5 mmol) dropwise *via* syringe. This mixture was allowed to stir for 30 minutes, at which point it was allowed to warm to room temperature, and then recooled to – 78 °C. Once the solution had cooled, bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol) was added to the resultant enolate in a dropwise manner. This solution was allowed to warm to room temperature over a period of 18 hours. The crude reaction mixture was extracted with saturated ammonium chloride (3 x 10 mL), water (2 x 10 mL), and brine (2 x 10 mL), dried over magnesium sulfate, and the solvent was removed *en vacuo*. Obtained after column chromatography (80 % hexane: 20% diethyl ether) was **10** (1.41 g, 83 %) as a colorless oil.

^{1}H δ 6.0-5.9 (1H, m), 5.8-5.7 (1H, m), 5.5-5.4 (1H, m), 4.5-4.3 (4H, m), 2.45-2.35 (2H, m), 2.1-1.9 (2H, m).

^{13}C δ 144.5 (d, J = 8.1 Hz), 130.8 (d, J = 6.4 Hz), 122.5 (2, dq, J = 276.7, 11.3 Hz), 120.65 (d, J = 9.1 Hz), 109.1 (d, J = 5.7 Hz), 64.2 (2, dq, J = 38.1, 5.4 Hz), 21.8 (s), 21.3 (s).

^{31}P δ - 6.38.

3.2.8b Method 2

After adding 2-cyclohexen-1-one (0.48 mL, 5 mmol) to a solution of LDA (5.5 mmol) at – 78 °C prepared according to the general procedure, the resulting enolate was treated with bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol). The solution was allowed to warm to room temperature over a period of 24 hours. After standard workup and purification, the desired product (1.03 g, 61%) was obtained as a light oil.

3.2.9 **1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]-5-methyl-1,5-cyclohexadiene (11)**

3.2..9a Method 1

To a solution of LDA (5.5 mmol) prepared in accordance with the general procedure was added 3-methyl-2-cyclohexen-1-one (5 mmol, 0.58 mL). After the requisite warming and cooling cycle, the resulting enolate was treated with bis(2,2,2-trifluoroethyl) phosphorochloridate (0.97 mL, 5.5 mmol). This solution was allowed to warm to room temperature over 18 hours, and was worked up and purified according to general procedure. Obtained was 1.478 g (84%) of **11**.

^{1}H δ 5.55-5.52 (1H, m), 5.35-5.30 (1H, m), 4.45-4.35 (4H, m), 2.33-2.24 (2H, m), 2.15-2.05 (2H, m), 1.80 (3H, s), 1.24-1.18 (2H, m), 0.9-0.8 (2H, m).

^{13}C δ 146.2 (d, J = 8.5 Hz), 122.5 (2, dq, J = 276.7, 11.3 Hz), 117.0 (d, J = 5.1 Hz), 64.2 (2, dq, J = 38.1, 5.4 Hz), 28.8 (s), 24.2 (d, J = 12.4 Hz), 23.0 (s).

^{31}P δ - 6.38.

3.2.10 **1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]-1,4-cyclopentadiene (12)**

3.2.10a Method 1

After addition of 2-cyclopenten-1-one (0.42 mL, 5 mmol) to a solution of LDA (5.5 mmol) in 25 mL of THF at – 78 °C prepared according to the general procedure, the resulting enolate was treated with bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol). After the addition was complete, the reaction mixture was allowed to warm to room temperature over a period of 18 hours. Standard workup produced **12** (70% by GC).

^{31}P δ -6.41.

3.2.11 **1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]-4-methyl-1,4-cyclopentadiene (13)**

3.2.11a Method 1

3-methyl-2-cyclopenten-1-one (0.50 mL, 5 mmol) was added dropwise *via* syringe to a solution of LDA (5.5 mmol) in THF at –78 °C, which was prepared according to the general procedure. After the addition was complete, the reaction mixture was warmed and cooled in accordance with the general procedure, and subsequently treated with bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol). This mixture was allowed to warm to room temperature over a period of 18 hours, and standard workup produced **13** (72% by GC).

31P δ -6.22.

3.2.12 **1-[[bis(2,2,2-trifluoroethoxy)phosphinyl]oxy]-1,6-cycloheptadiene (14)**

3.2.12a Method 1

In accordance with general procedure, 2-cyclohepten-1-one (0.56 mL, 5 mmol) was treated sequentially with LDA (5.5) in THF (25 mL) at –78 °C and bis(2,2,2-trifluoroethyl)phosphorochloridate (0.97 mL, 5.5 mmol). The resulting mixture was treated in accordance with general procedure to yield **14** (67% by GC) as a crude mixture.

3.2.13 **1-phenyl-1,5-cyclohexadiene (22)**

3.2.13a Method 1, General Method for Suzuki Couplings of Dienyl Phosphates and Phenylboronic acid.

A solution of nickel (0) catalyst in toluene (8 mL) was generated *in situ* by reduction of [1,1'-bis(diphenylphosphino)-ferrocene]dichloronickel (II) (0.0213 g, 0.03 mmol) by *n*-butyllithium (0.188 mL of a 1.6 M solution in hexane, 0.3 mmol) *via* dropwise addition at room temperature. The reaction flask was purged for 10 minutes with argon prior to the reduction. This mixture was allowed to stir for 10 minutes, at which time it was cannulated into a pressure tube containing dienyl phosphate (2.5 mmol), anhydrous K_3PO_4 (1.06 g, 5 mmol), phenylboronic acid (.305 g, 2.5 mmol), and 1, 1' – bis(diphenylphosphino) ferrocene (dppf) (0.045 g, 0.08 mmol), and toluene (2 mL). This tube was then purged for an additional 30 minutes with argon and sealed. The contents of the pressure tube were stirred in an oil bath at 90 °C for 72 hours. The crude reaction mixture was diluted with ether (10 mL) and extracted with water (2 x 4 mL), and brine (2 x 4 mL) and the solvent was removed by rotary evaporation. Column chromatography (80% hexane/20 % diethyl ether) produced **22** (0.090 g, 38%) as an impure yellow oil. Further efforts to generate pure product were unsuccessful.

3.2.13b Method 2

To a pressure tube prepared according to the general procedure from the general procedure was added zinc powder (0.2 g, 3 mmol), and the tube was purged with argon for 30 minutes. The tube was then sealed and heated in an oil bath at 90 °C for a period of 48 hours. Standard workup and purification yielded desired product (0.077 g, 32%) as a colorless oil.

^{1}H δ 7.5-7.2 (5H, m), 6.4-6.3 (1H, m), 6.2-6.1 (1H, m), 6.0-5.9 (1H, m), 2.5-2.4 (2H, m), 2.4-2.3 (2H, m).

^{13}C δ 142.3 (s), 141.8 (s), 127.9 (d, J = 12.2 Hz), 125.2 (s), 123.8 (s), 122.1 (s), 121.7 (s), 26.6 (s), 24.8 (s).

3.2.13c Method 3

The general procedure was repeated exactly with the one exception of the use of sodium hydroxide (0.2 g) as the base. No coupling turnover was recorded after 72 hours heating and standard workup and purification.

3.2.13d Method 4

The pressure tube was prepared according to the general procedure with the exception of dimethoxyethane being used as the solvent. Standard workup and purification yielded no coupling turnover.

3.2.13e Method 5

The general procedure was followed with the exception that the pressure tube was heated to 110 °C for 72 hours. No desired product was obtained after standard workup and purification.

3.2.14 **1-phenyl-5-methyl-1,5-cyclohexadiene (23)**

3.2.14a Method 1

To a pressure tube which was purged with argon and flame dried was added **11** (0.89 g, 2.5 mmol), dppf (0.084 g, 0.15 mmol), 1.06 g anhydrous K_3PO_4 (5 mmol), 0.610 g (5 mmol) phenylboronic acid, and 0.2 g zinc powder. Toluene (2 mL), and the Ni(0) catalyst solution, which was prepared according the general procedure, were added *via* syringe. The tube was then purged for an additional 30 minutes and then sealed and heated at 90 °C for 72 hours. Desired product (0.187 g, 44%) was obtained as an impure colorless oil after standard workup and column chromatography. Further attempts at purification were unsuccessful.

^{1}H δ 7.5-7.2 (5H, m), 6.4-6.3 (1H, m), 6.2-6.1 (1H, m), 6.0-5.9 (1H, m), 2.5-2.4 (2H, m), 2.4-2.3 (2H, m).

^{13}C δ 142.3 (s), 141.8 (s), 133.4 (s), 127.9 (s), 125.2 (s), 123.8 (s), 122.1 (s), 121.7 (s), 26.6 (s), 24.8 (s), 23.0 (s).

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Figure **S – 1** ^{1}H NMR of Compound **1**

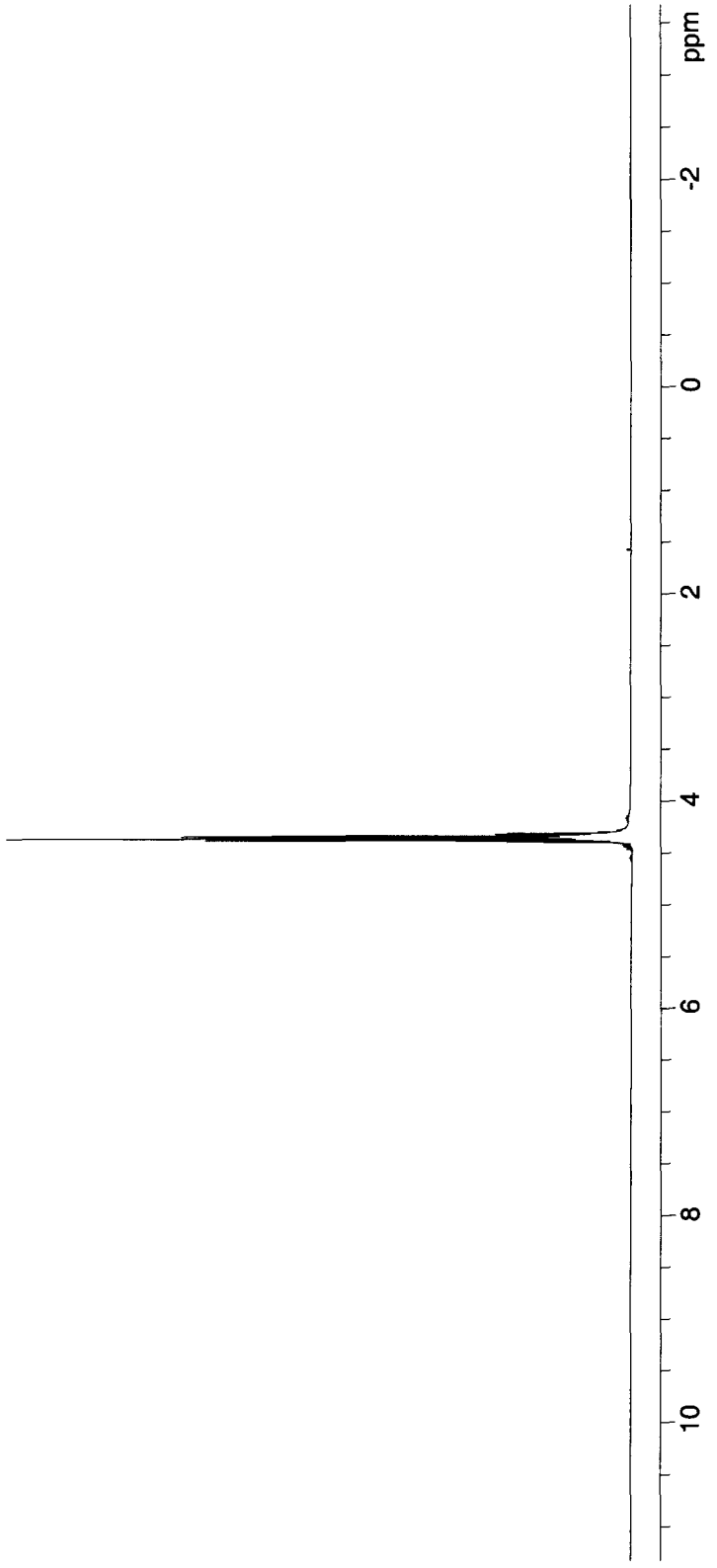


Figure **S – 2** ^{1}H NMR of Compound **1** (expanded)

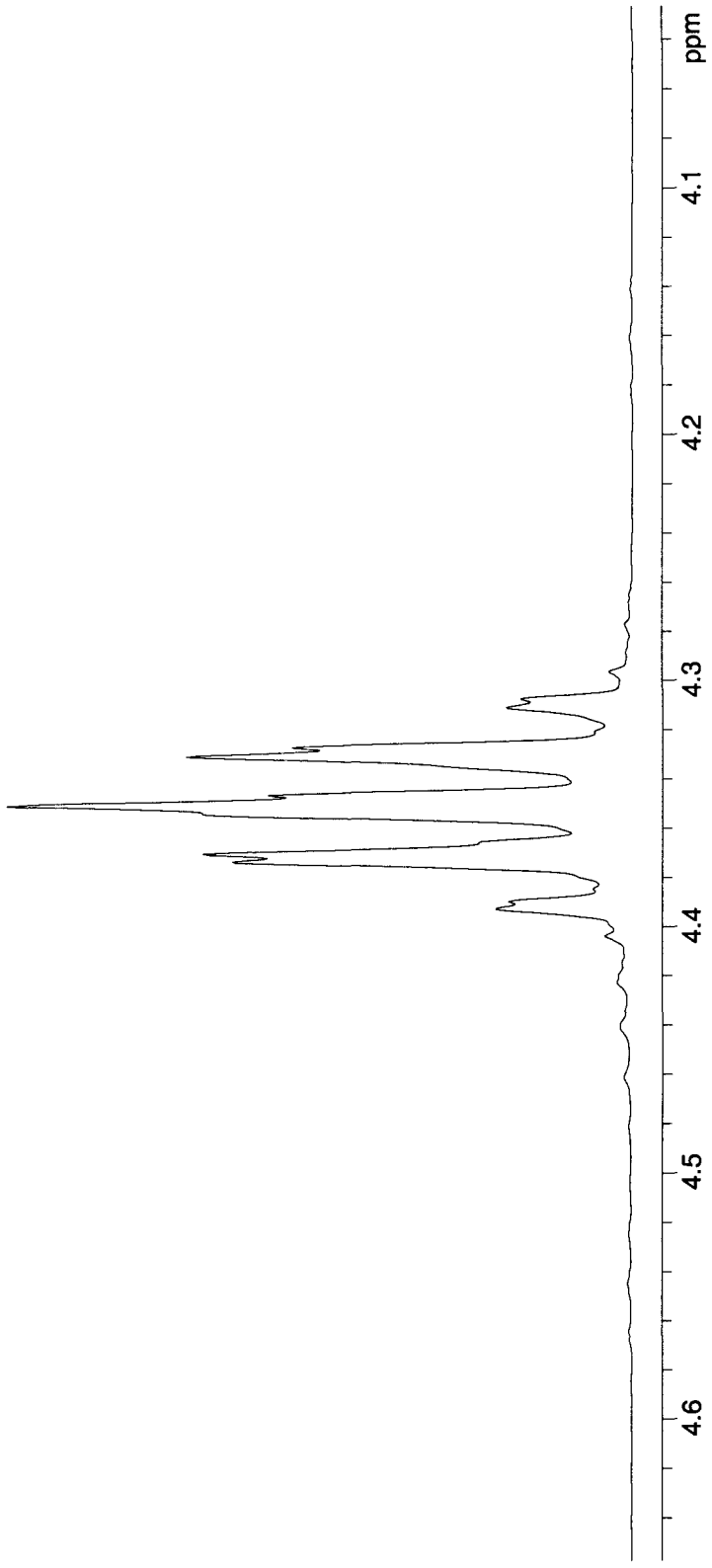


Figure **S – 3** ^{13}C NMR of Compound **1**

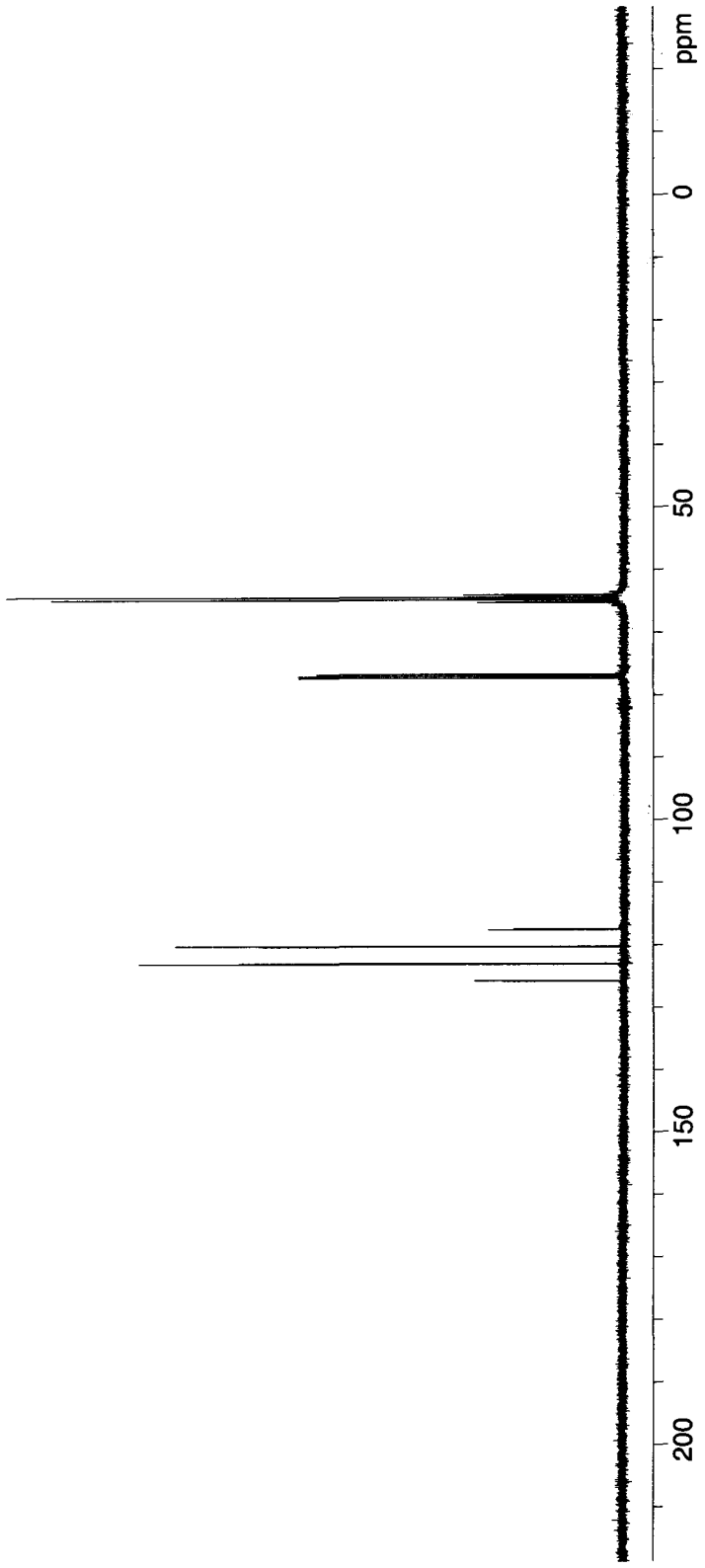


Figure **S – 4** ^{13}C NMR of Compound **1** (expanded)

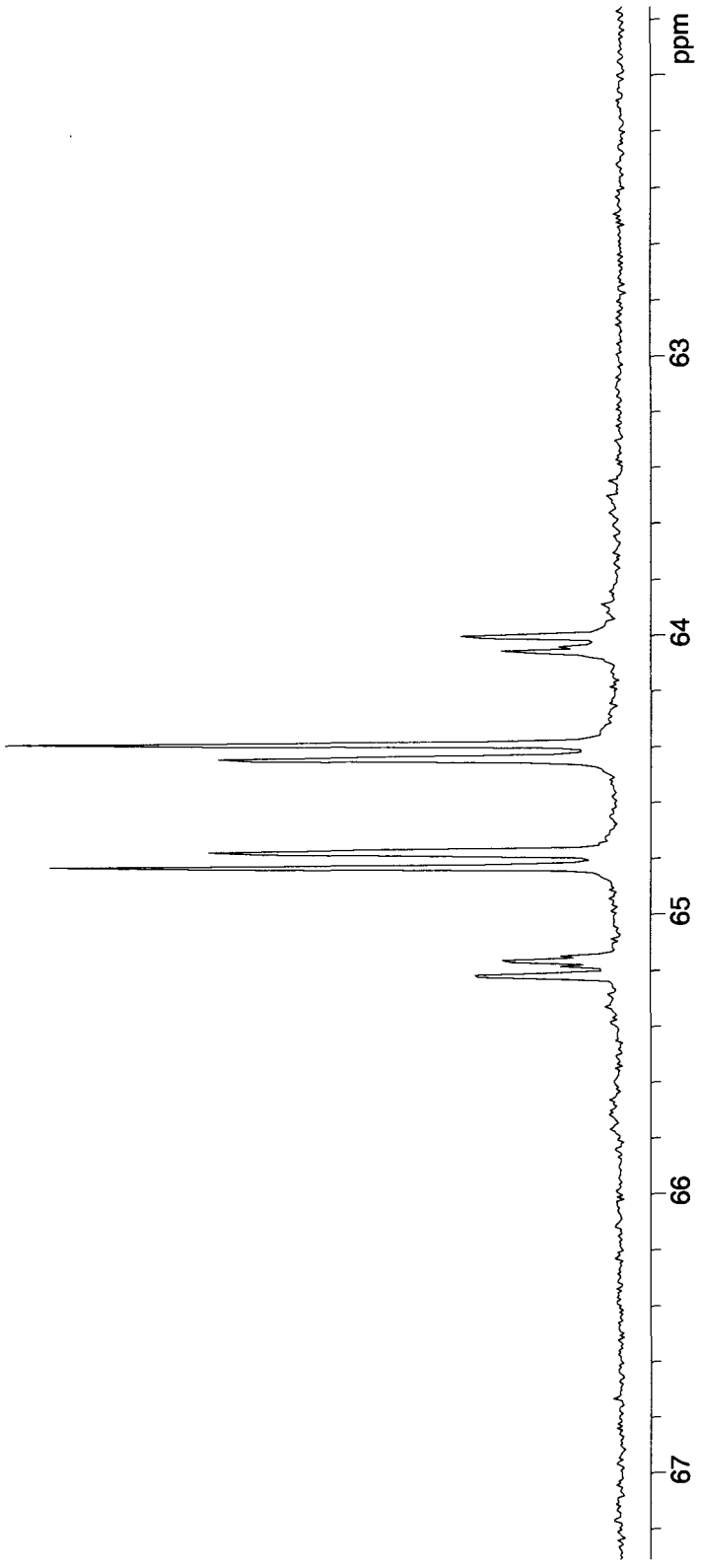


Figure **S – 5** ^{13}C NMR of Compound **1** (expanded)

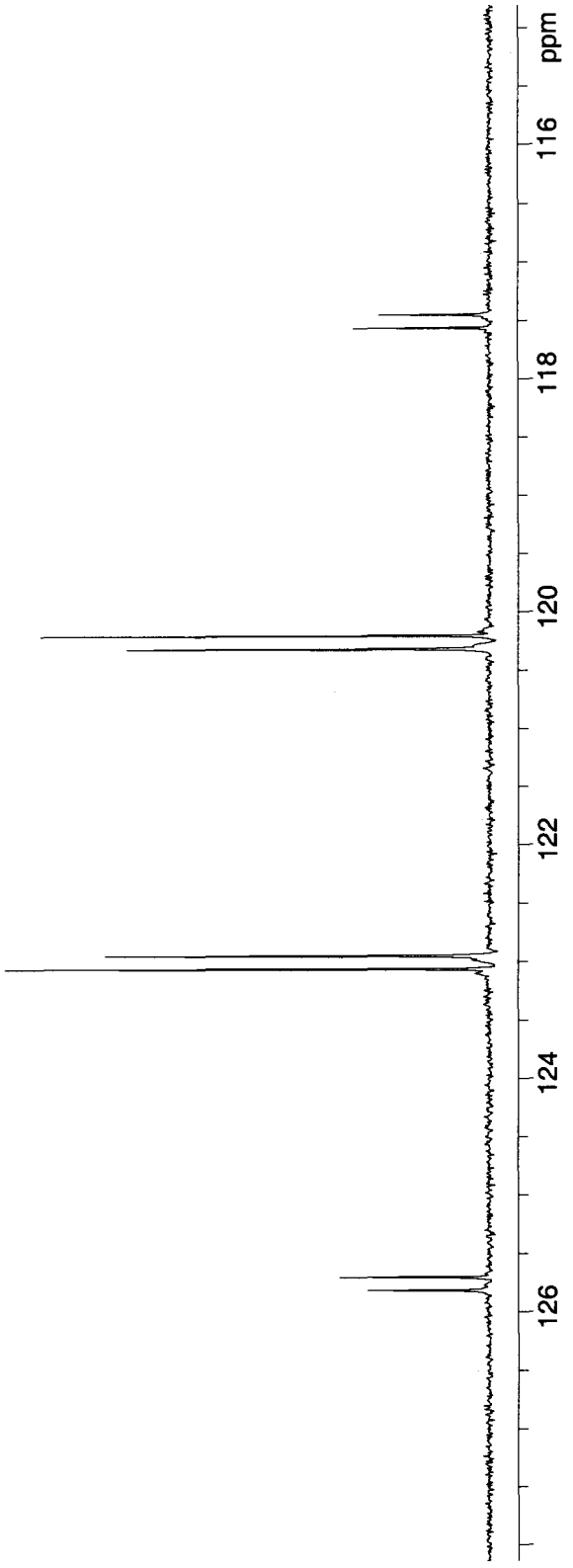


Figure **S – 6** ^{31}P NMR of Compound **1**

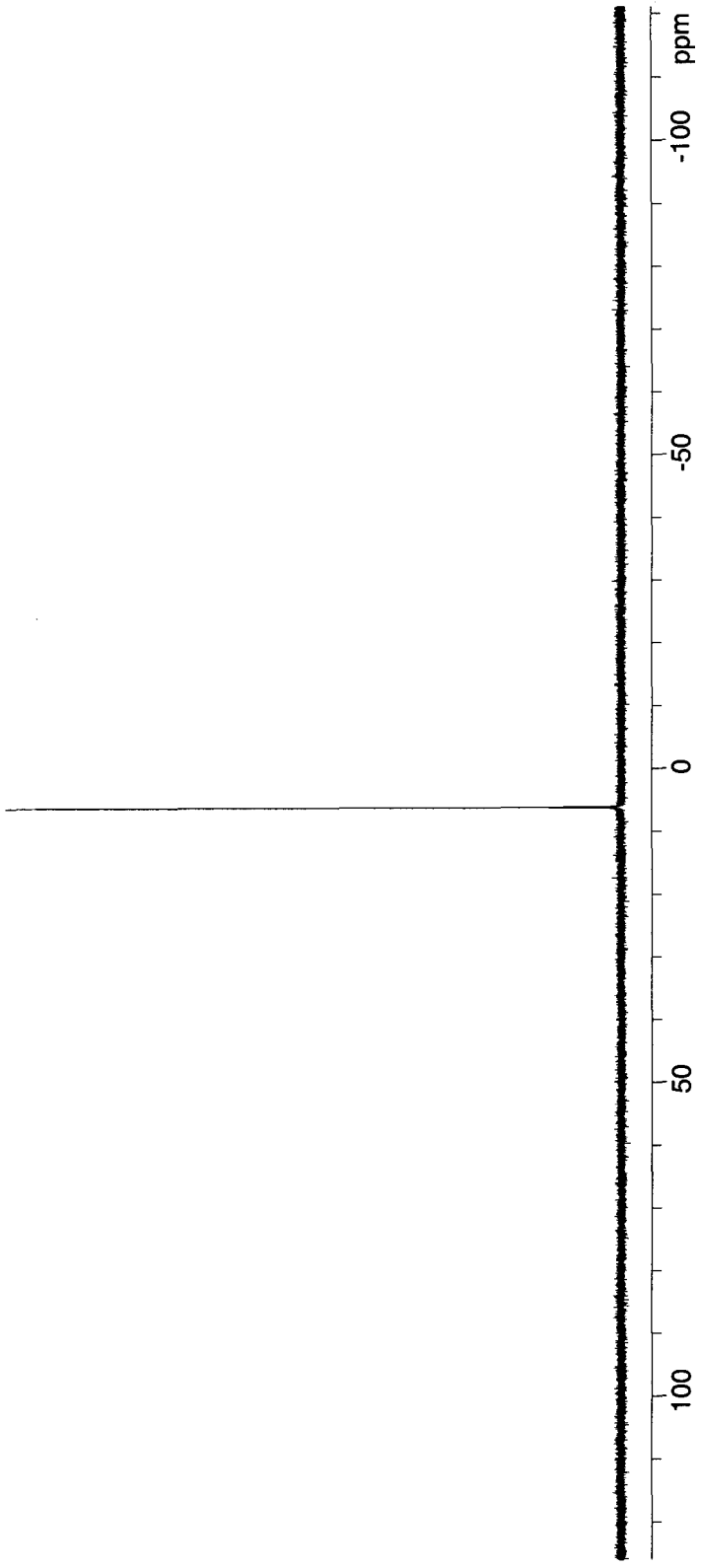


Figure **S – 7** ^{1}H NMR of Compound **2**

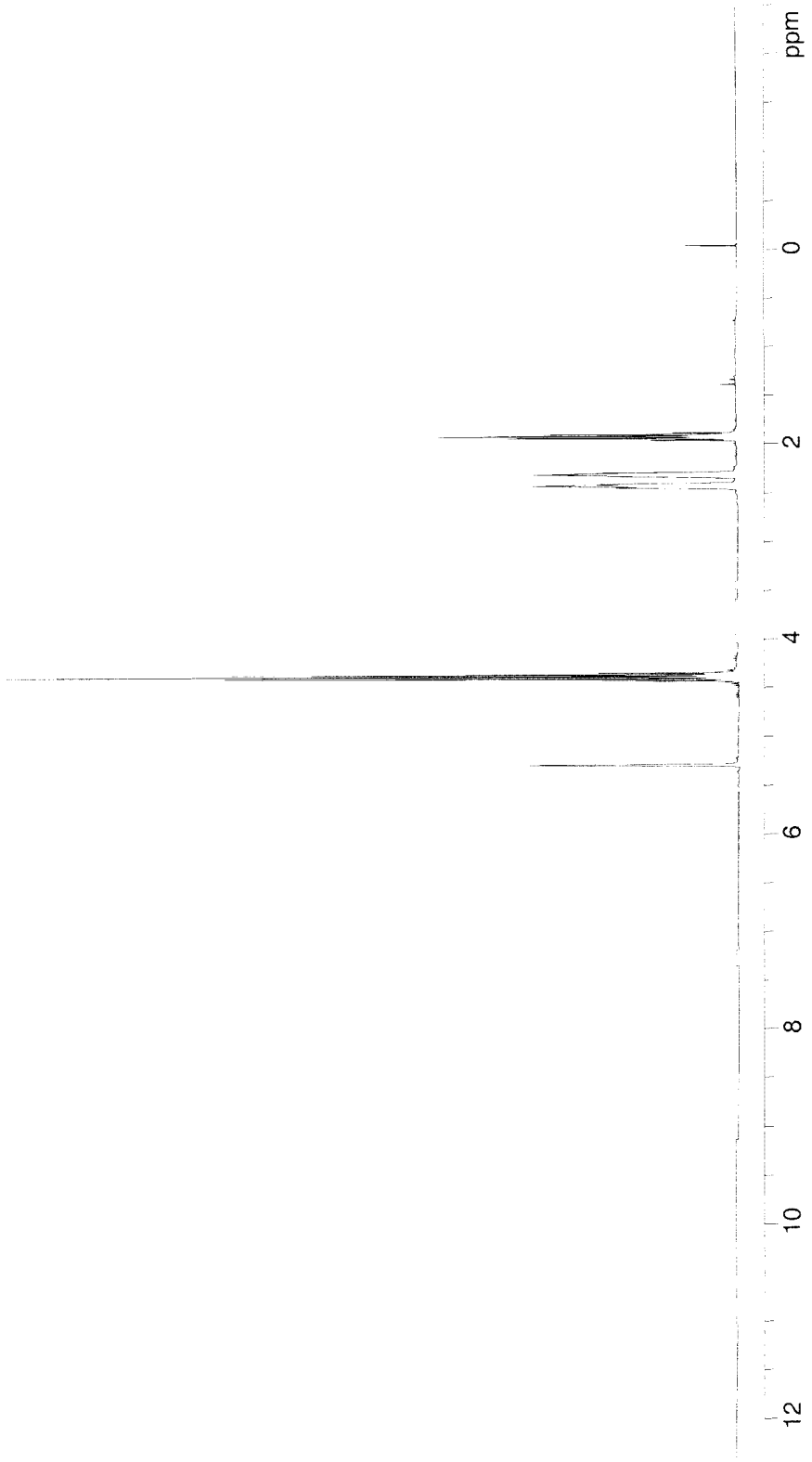


Figure **S – 8** ^{13}C NMR of Compound **2**

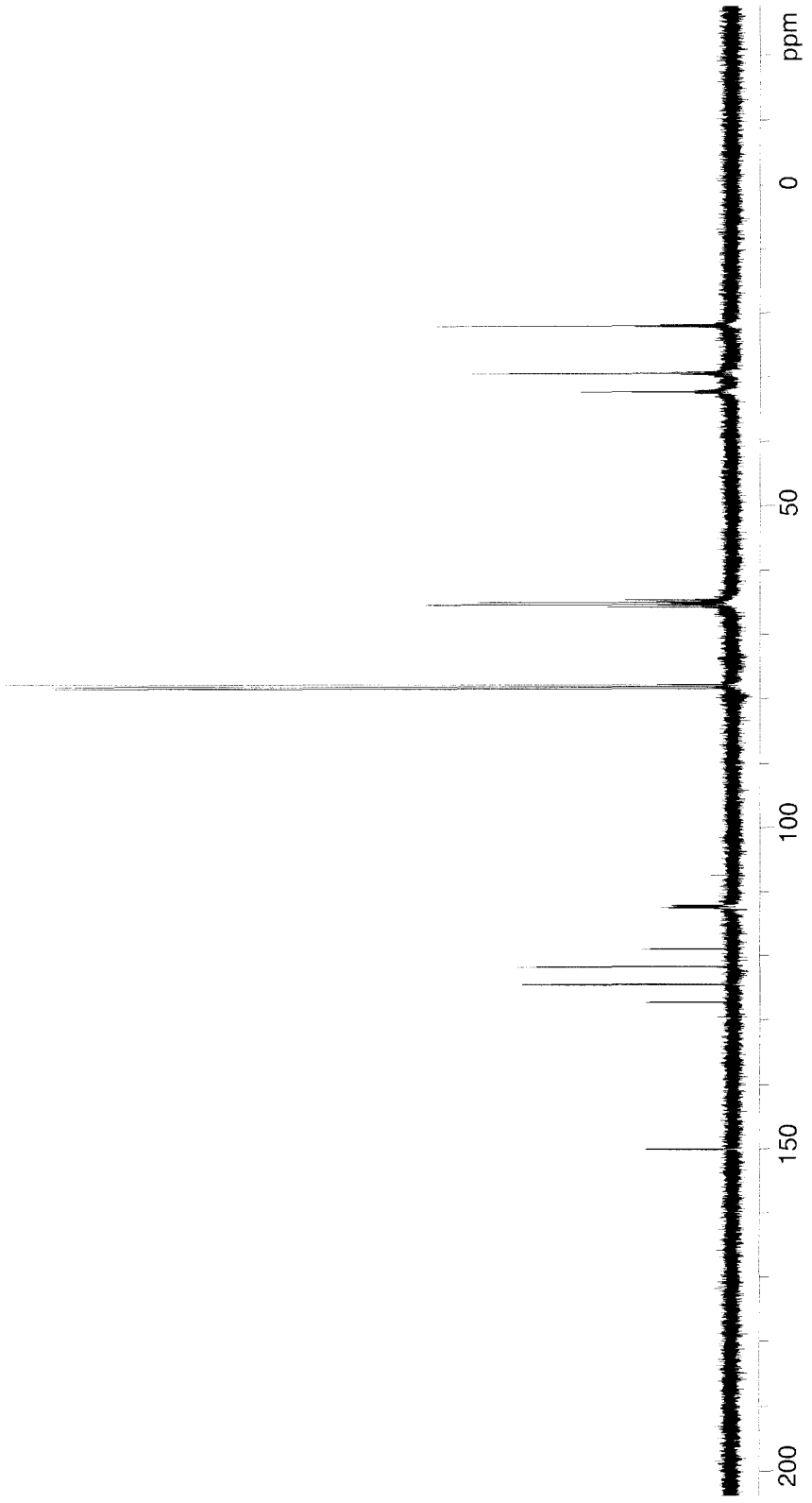


Figure **S – 9** ^{31}P NMR of Compound **2**

Figure **S – 10** ^{1}H NMR of Compound **3**

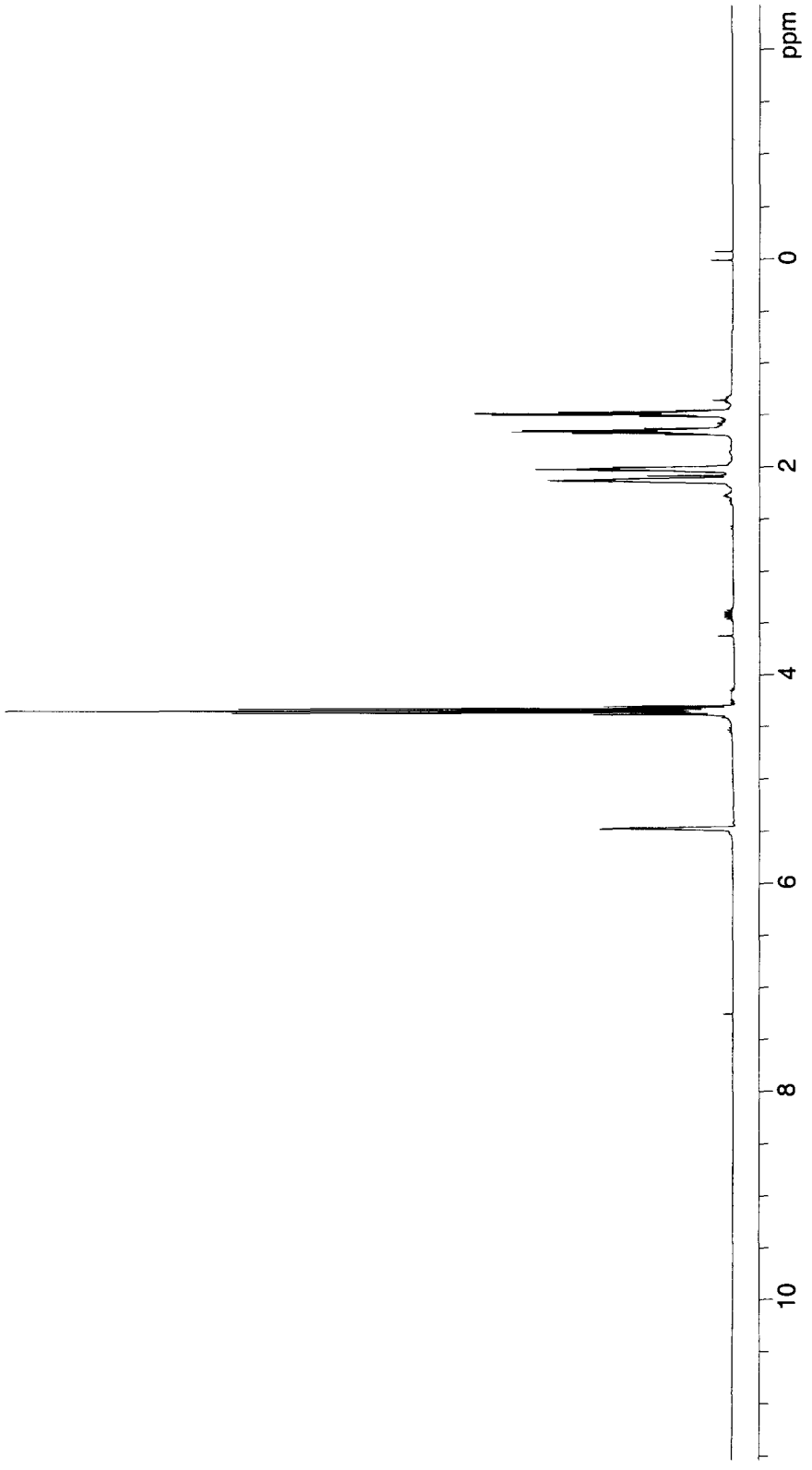


Figure **S – 11** ^{13}C NMR of Compound **3**

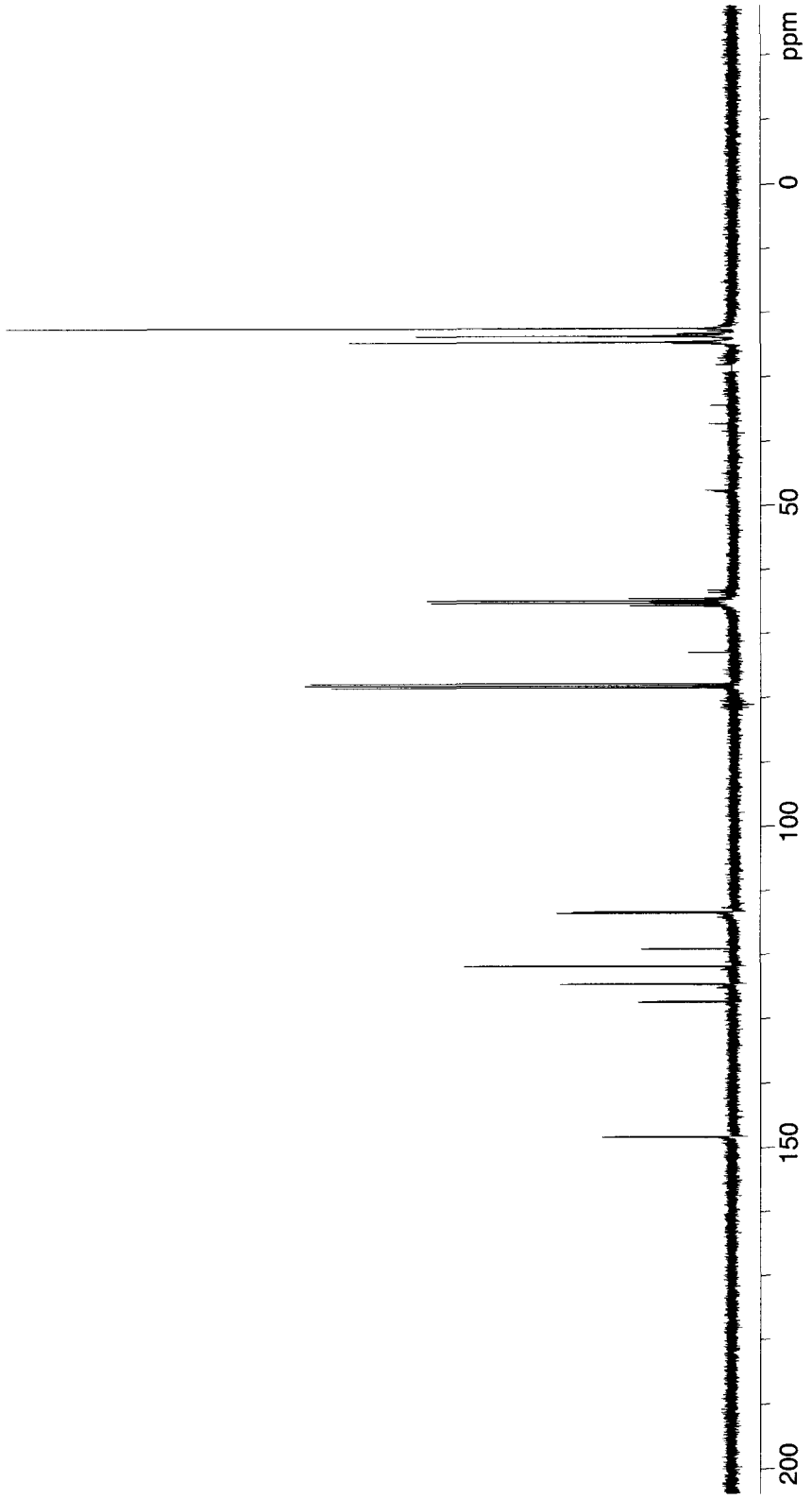


Figure **S – 12** ^{31}P NMR of Compound **3**

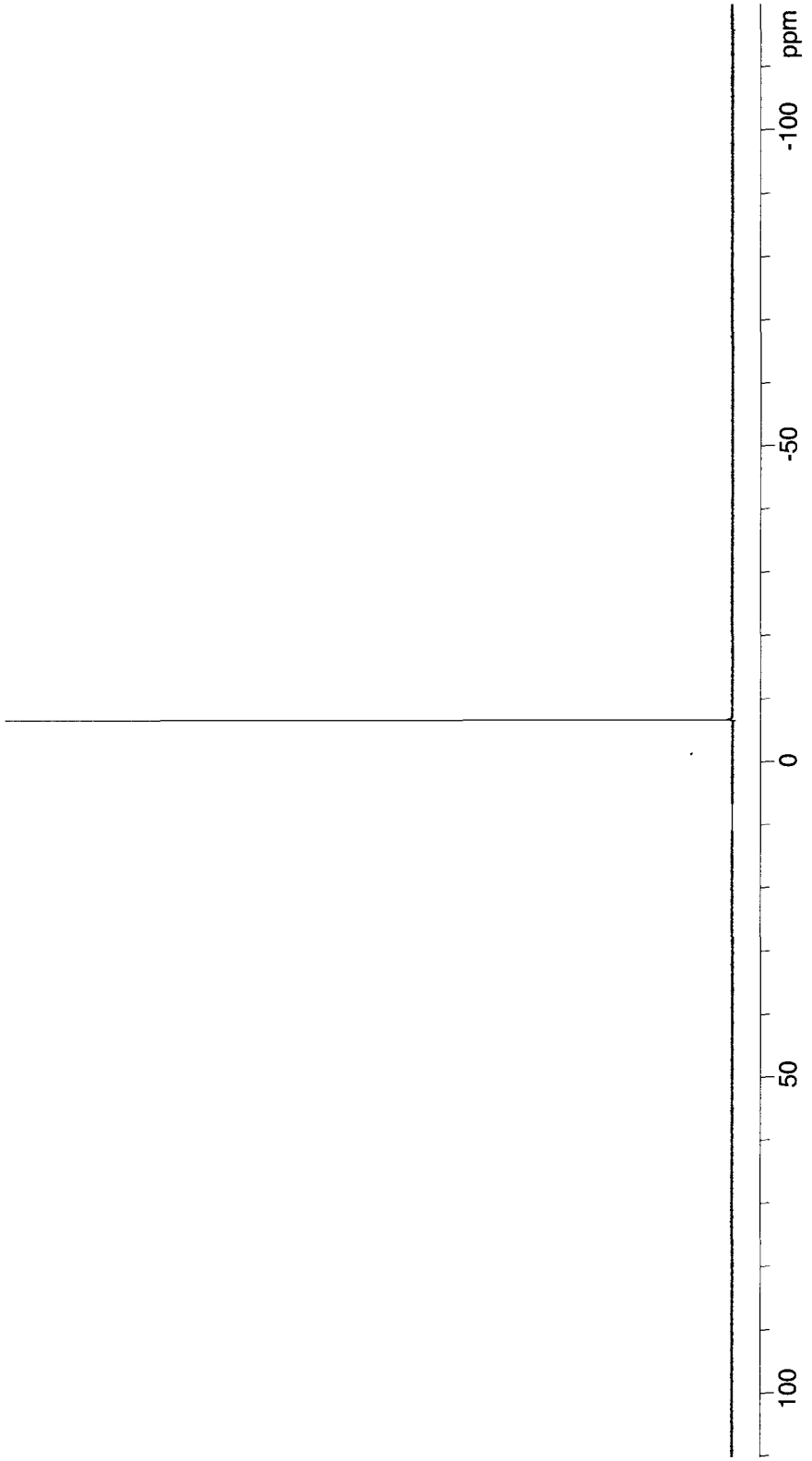


Figure **S – 13** ^{1}H NMR of Compound **4**

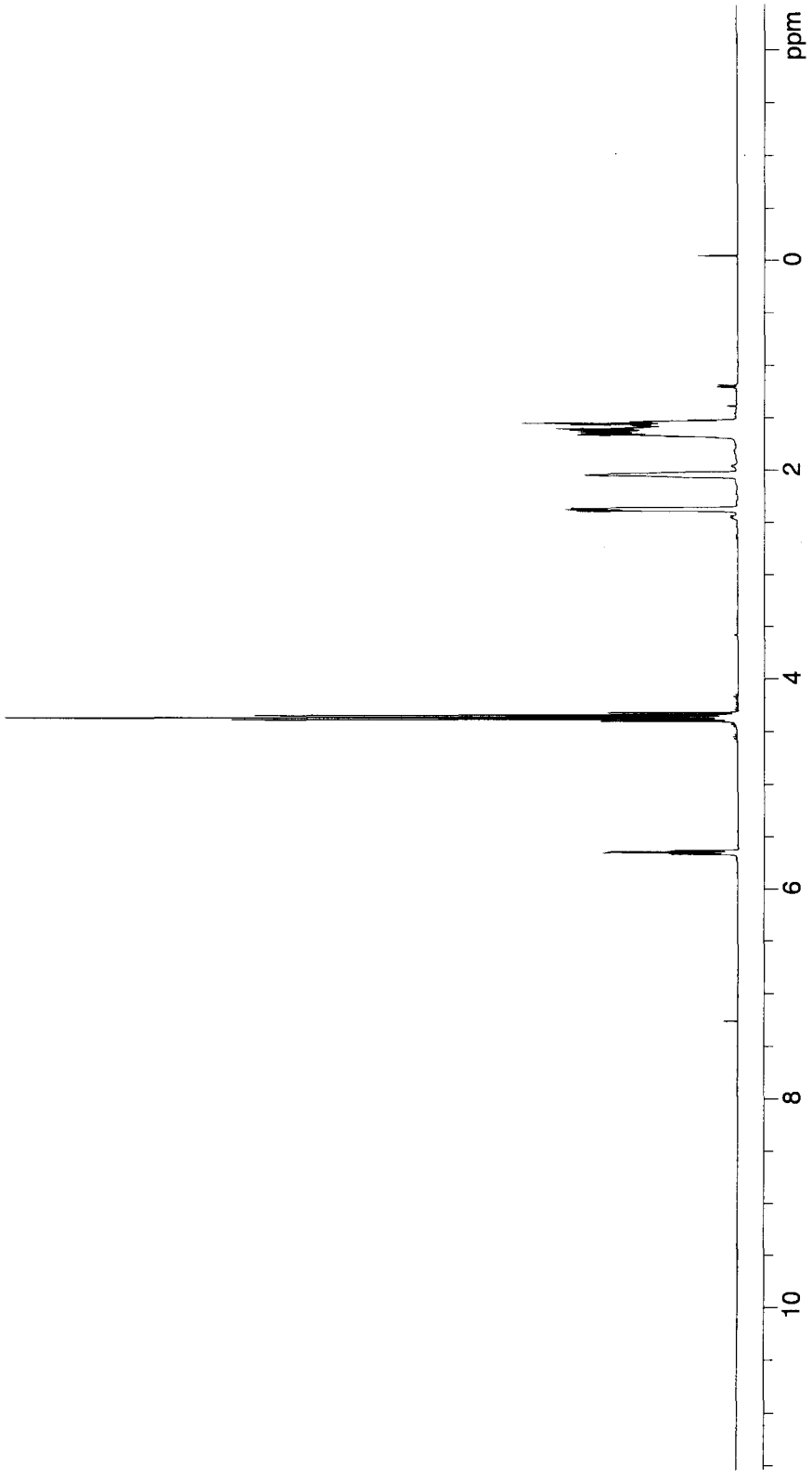


Figure **S – 14** ^{13}C NMR of Compound **4**

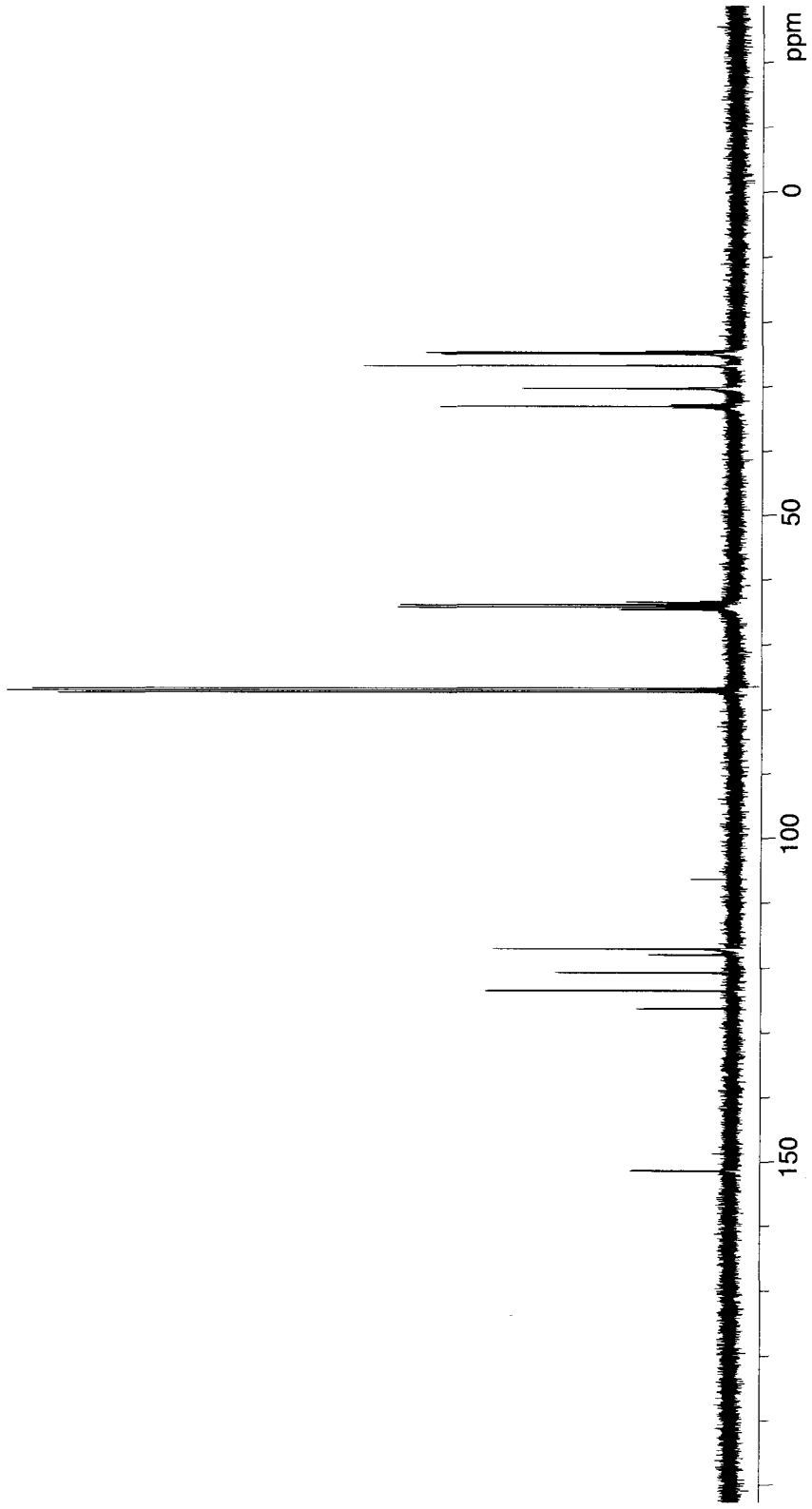


Figure **S – 15** ^{31}P NMR of Compound **4**

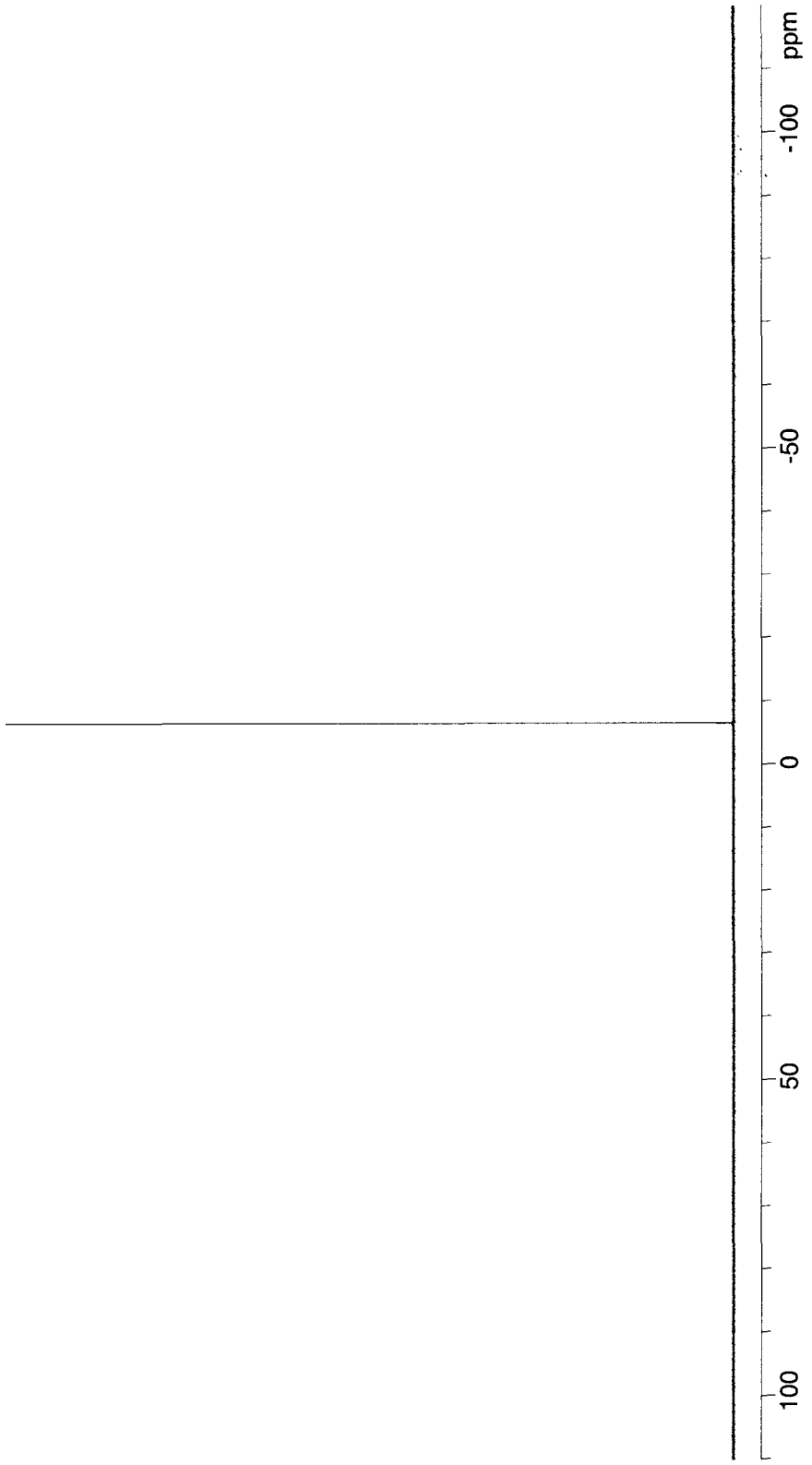


Figure **S – 16** ^{1}H NMR of Compound **6**

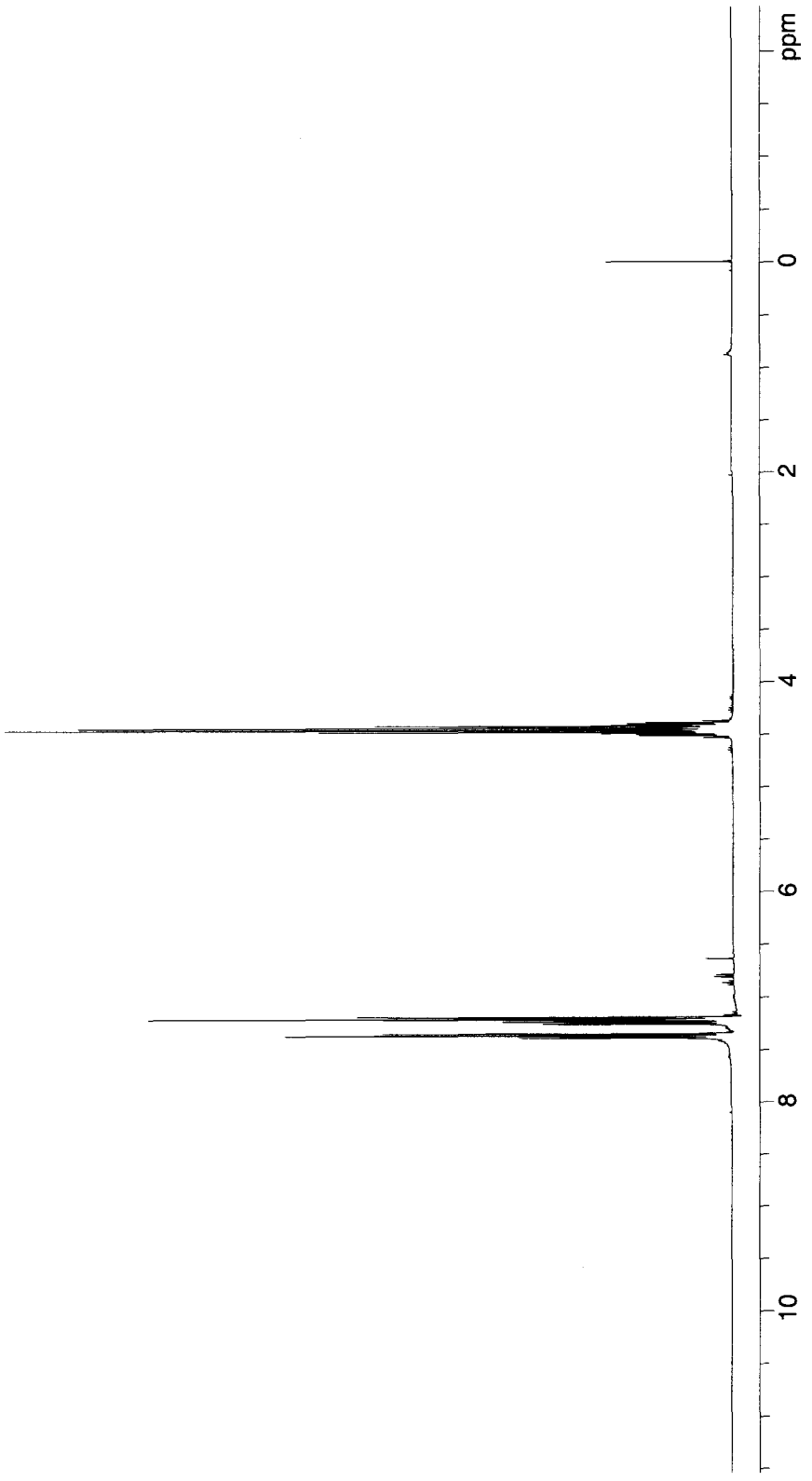


Figure **S – 17** ^{13}C NMR of Compound **6**

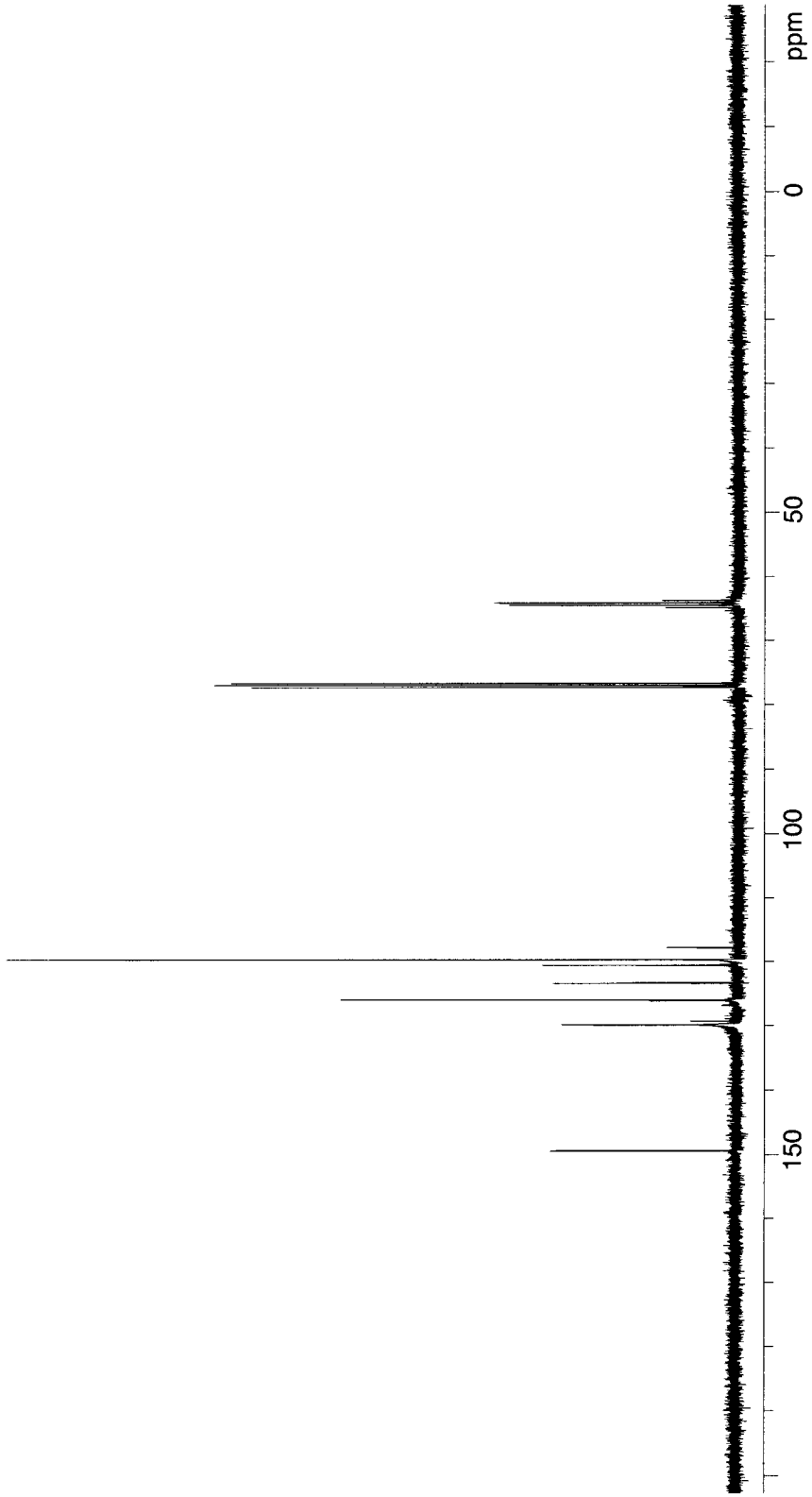


Figure **S – 18** ^{31}P NMR of Compound **6**

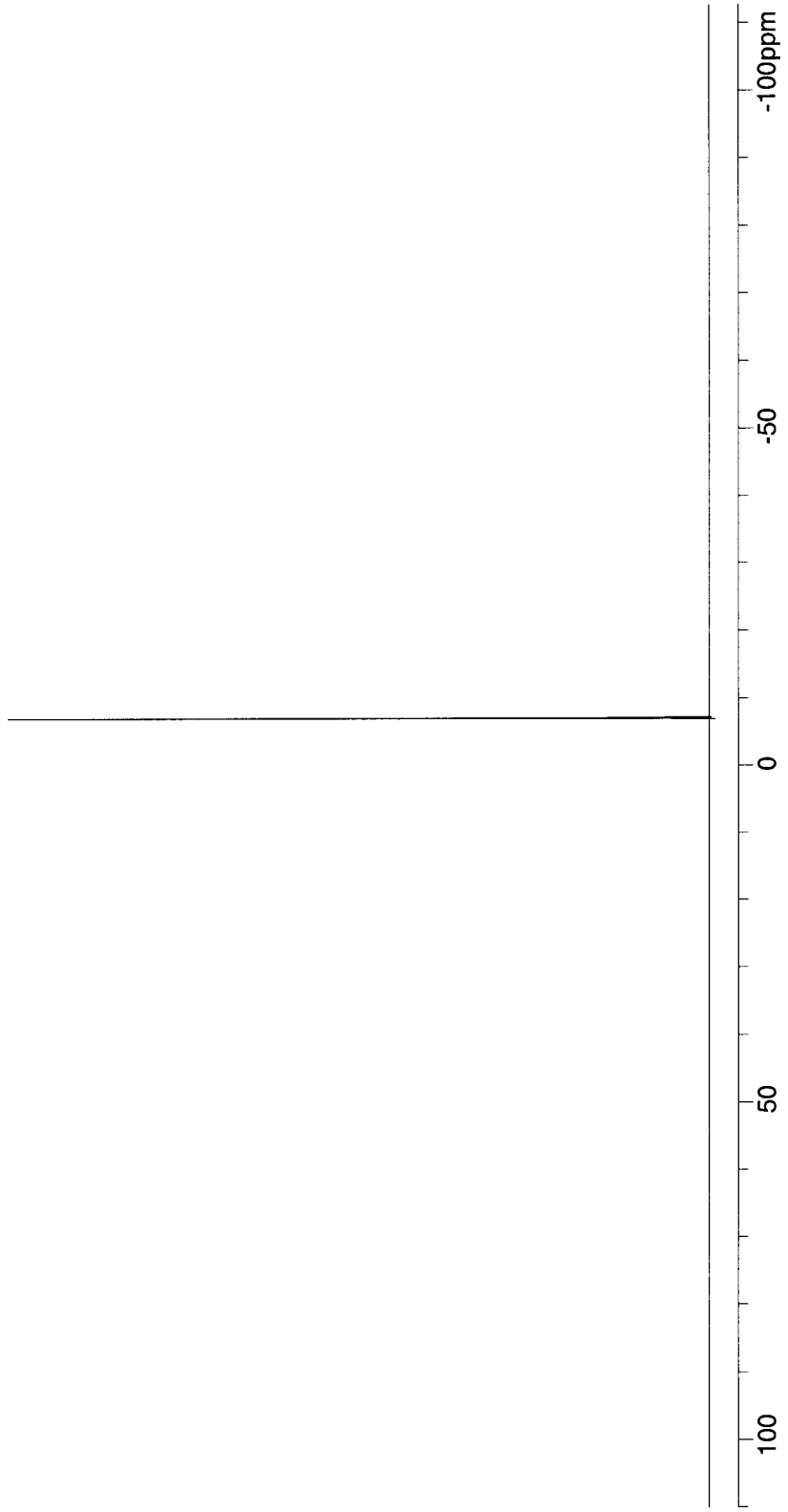
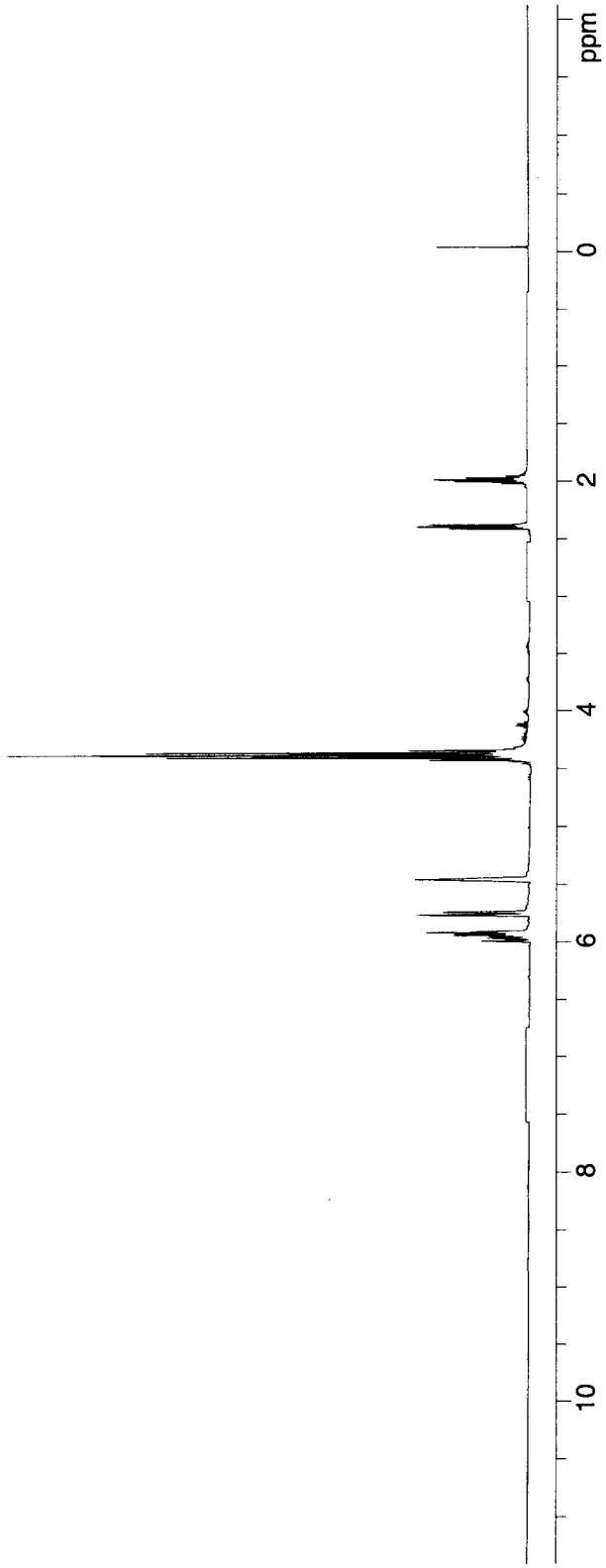


Figure **S – 19** ^{1}H NMR of Compound **10**



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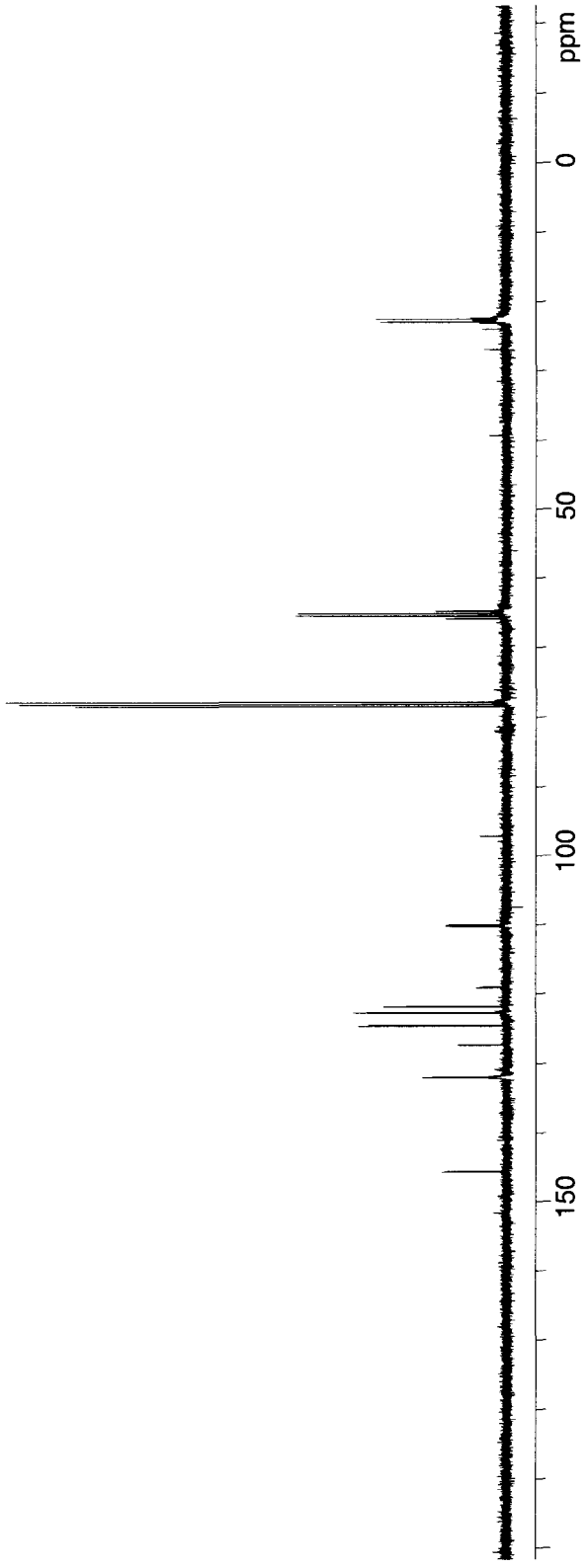

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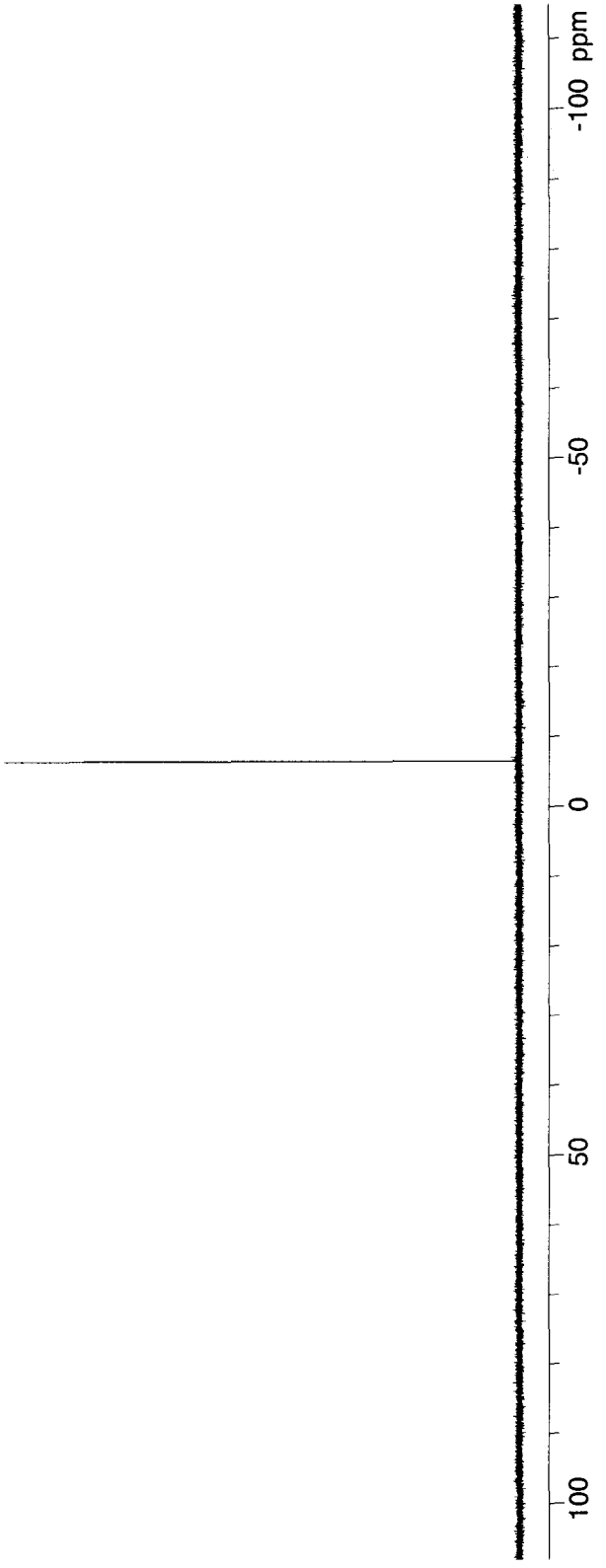

Figure **S – 22** ^{1}H NMR of Compound **11**

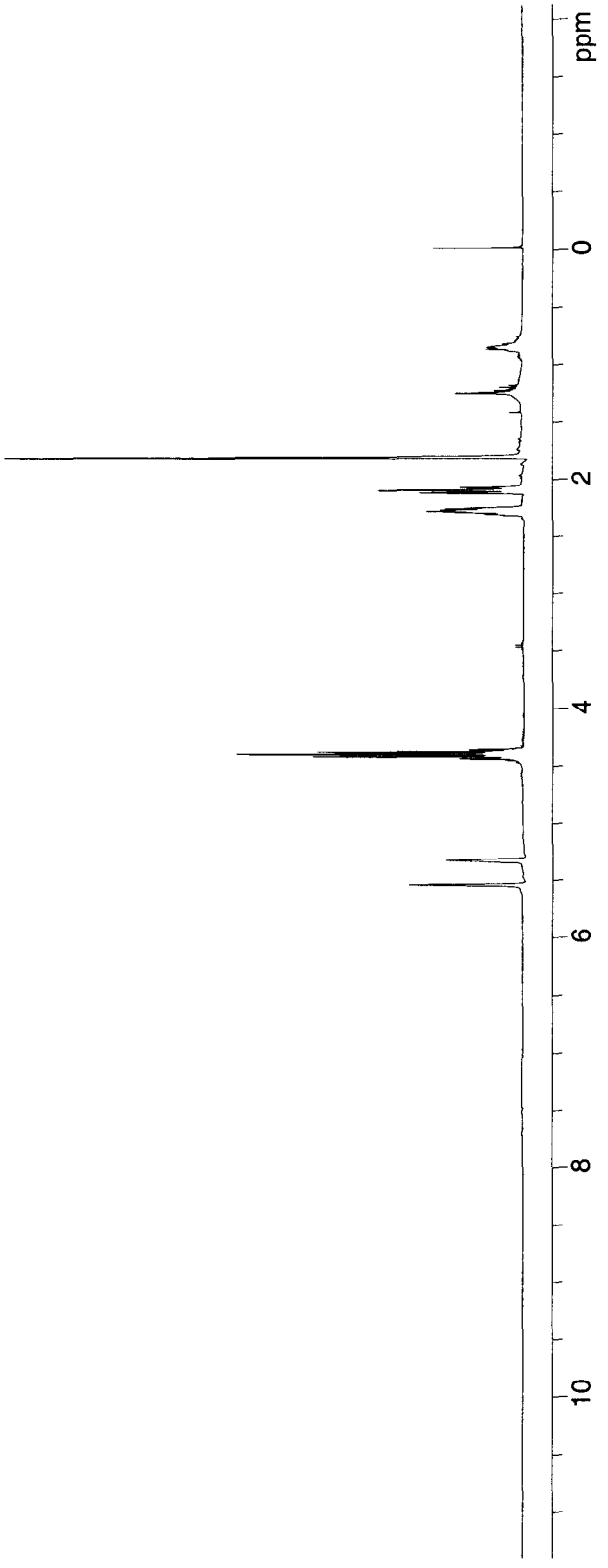

Figure **S – 23** ^{13}C NMR of Compound **11**

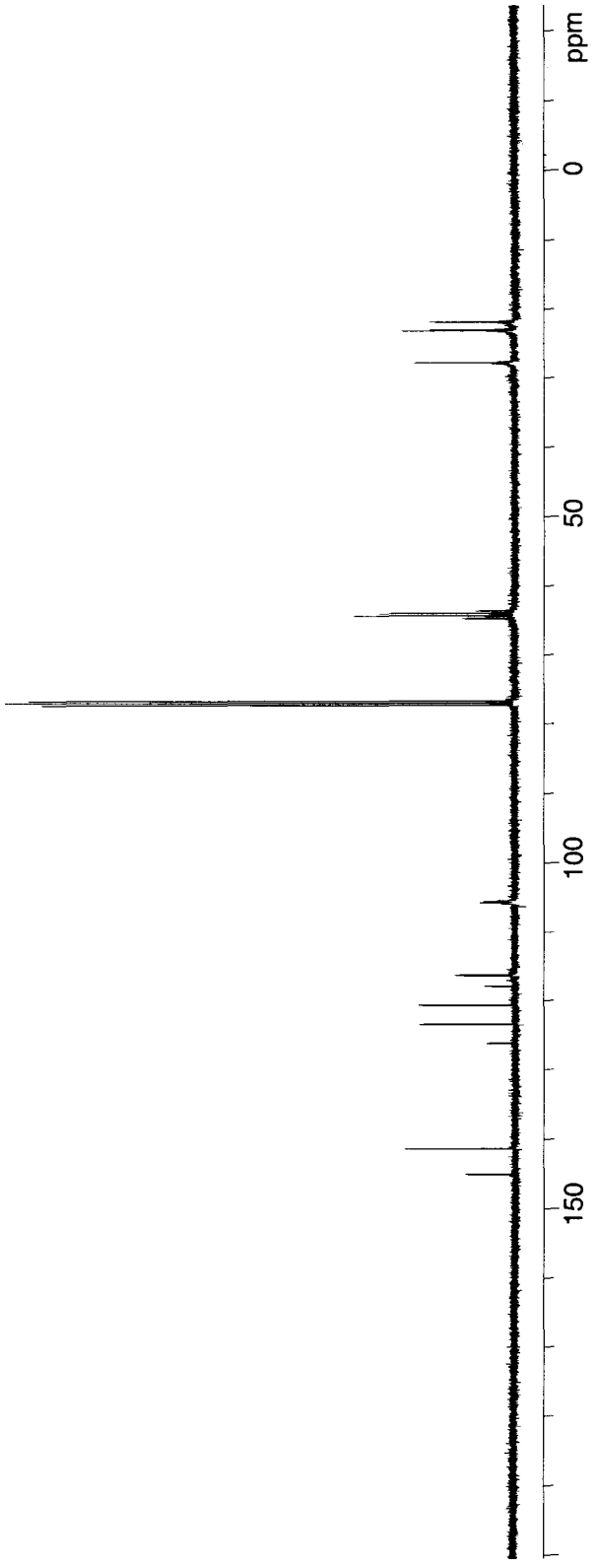

Figure **S – 24** ^{31}P NMR of Compound **11**

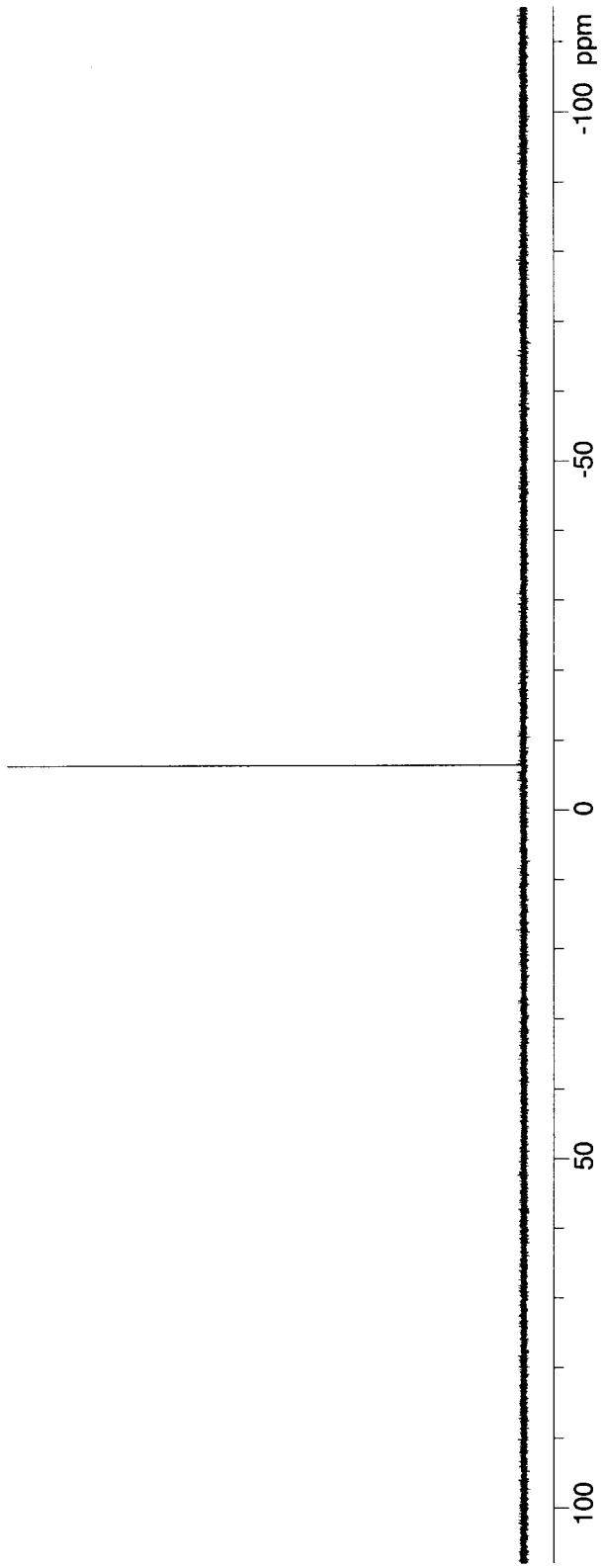

Figure **S – 25** ^{1}H NMR of Compound **22**

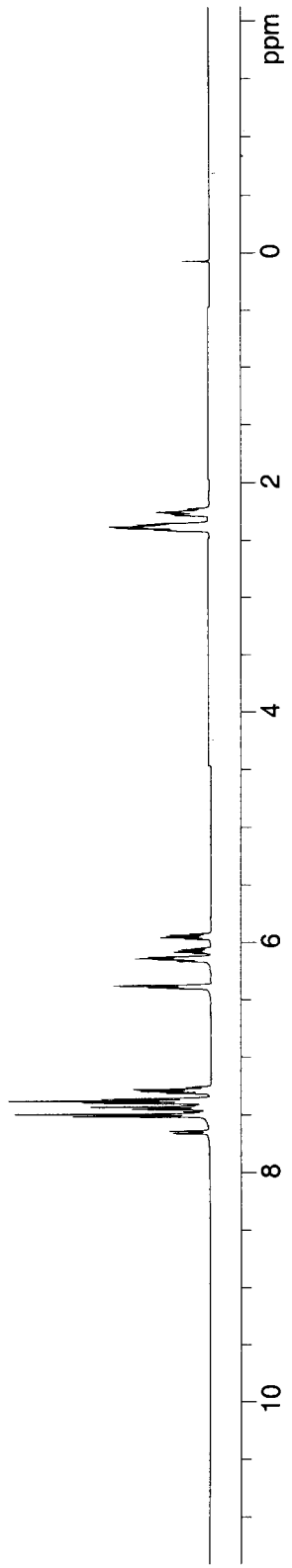

Figure **S – 26** ^{13}C NMR of Compound **22**

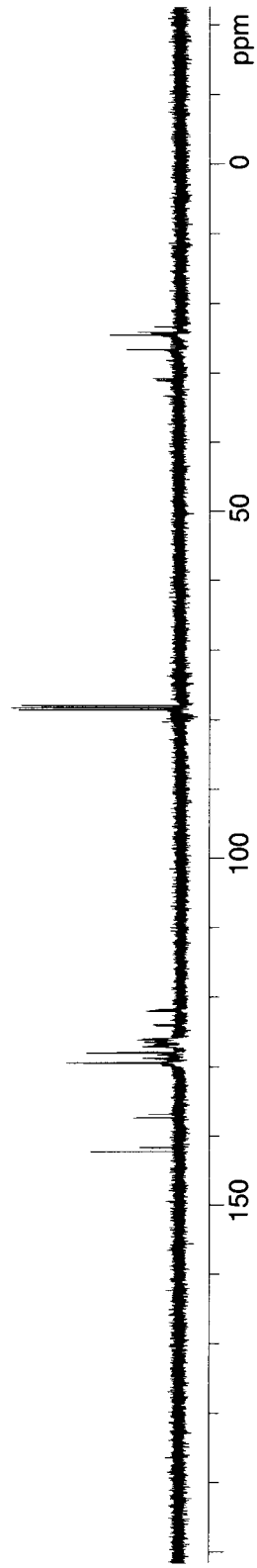

Figure **S – 27** ^{1}H NMR of Compound **23**

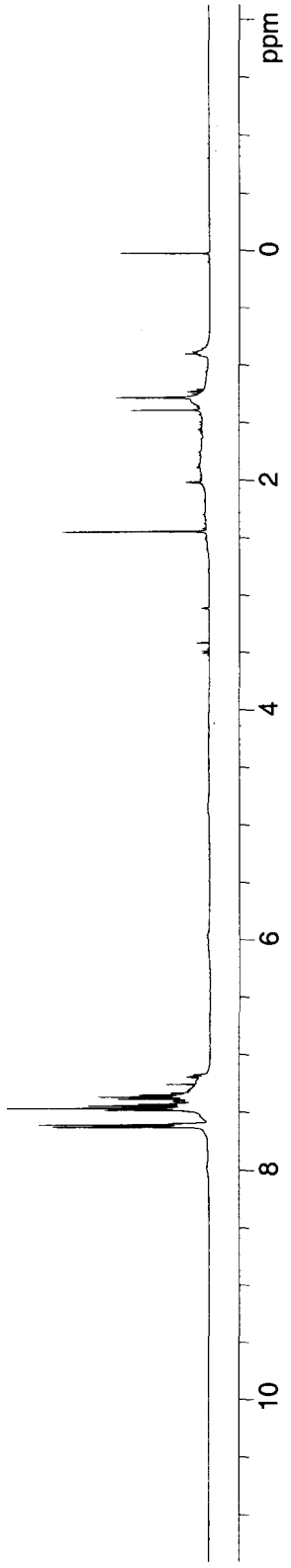

Figure **S – 28** ^{13}C NMR of Compound **23**