Recent Advances in Heteroatom-Stabilized Carbanion Chemistry

Student: Priyabrata Das
Supervisor: Dr. James McNulty

A Thesis Submitted to the

School of Graduate Studies

In Partial Fulfillment of The Requirements for The Degree of

Doctor of Philosophy

McMaster University

August 2009

Hamilton, ON

DOCTOR OF PHILOSOPHY (2009)

Title: Recent Advances in Heteroatom-Stabilized Carbanion Chemistry

Author: Mr. Priyabrata Das

Supervisor: Dr. Jim McNulty

Number of pages: 221

ABSTRACT

An efficient, stereoselective method for the synthesis of α-phosphonoenamines based on a modified Peterson olefination was developed. The carbanion derived from Diethyl 1-dimethylamino-1-trimethylsilylmethanophosphonate reacted with aromatic or aliphatic aldehydes selectively eliminating in Peterson fashion to deliver functionally rich α-phosphonoenamines.

A highly efficient method was developed for the one-carbon homologation of aldehydes to carboxylic acid derivatives employing the reaction of a 1,1-*bis*-dimethylphosphonate derivative with the aldehyde and controlled acid hydrolysis of the derived α-phosphonoenamine intermediate.

The reaction of bis(trimethylsilyl)chloromethane with *s*-BuLi was found to proceed via transmetallation rather than deprotonation yielding the nucleophilic bistrimethylsilylmethyl anion quantitatively which reacted readily with aldehydes providing a general entry to vinylsilanes.

The reaction of α–silylated ylides with non-enolizable aldehydes proceeded via selective Peterson-type elimination, in contrast to prior literature reports, providing a direct route to synthetically useful vinylphosphonium salts.

The chemoselective formation of trialkylbenzyl phosphoranes in water and their Wittig reaction with aromatic and aliphatic aldehydes provided a practical, stereoselective and environmentally benign route to valuable *trans*-stilbenes and alkenes. The synthesis of the phytoalexin resveratrol was described. In addition, the method allowed for a gram-scale synthesis of the anticancer agent DMU-212 utilizing no organic solvent at any stage.

A direct synthesis of 1,3-dienes and 1,3,5-trienes from the reaction of semi-stabilized ylides and a range of saturated and unsaturated aldehydes was reported in water as solvent, employing sodium hydroxide as base. The water-soluble phosphine oxide side product was removed simply by aqueous partitioning of the organic products.

ACKNOWLEDEGEMNTS

I would like to thank my supervisor Dr. James McNulty for the opportunity to pursue my PhD under his supervision. I have learned a lot from your extensive knowledge and I am also grateful to you for the confidence you have shown in me. I would also like to appreciate the support provided by Dr. Paul. Harrison, Dr. John Valliant and Dr. Fred Capretta.

I would like to thank my group members for their constant encouragement.

Finally, I would like to take the opportunity to thank my family members for their love and support during these often-difficult times.

LIST OF ABBREVIATIONS USED

THF	Tetrahydrofuran
DCM	Dichloromethane
TMS	Trimethylsilyl
LDA	Lithiumdiisopropylamide
n-BuLi	Primary-butyllithium
s-BuLi	Secondary-butyllithium
MeLi	Methyllithium
EtOAc	Ethyl acetate
NaOH	Sodium hydroxide
LiOH	Lithium hydroxide
Na_2SO_4	Sodium sulfate
$CDCl_3$	Deuterated chloroform

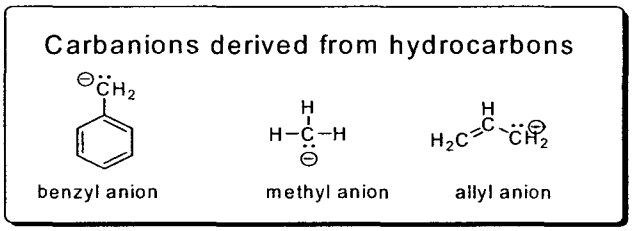
Table of Contents

Introduction and General Background:

Carbanions[1] have played a central role in modern synthetic organic chemistry from the beginnings of the subject. The many factors governing their formation, structure, stability and reactivity are amongst the principal foundations of organic chemistry. Carbanions were first generated as carbonyl stabilized intermediates as well as simple organozinc and subsequently organomagnesium reagents in the late 19^{th} to early 20^{th} century. More reactive oragnolithium reagents emerged later. Less reactive main group and transition metal functionalized carbanion equivalents have been employed mainly from the 1950's and 1970's respectively. Consequently, the chemistry of carbanions encompasses both classical name reactions such as Claisen, Michael and Grignard to more recent examples including Wittig, Peterson, Tsiju-Trost and many variations thereof. The extension to enantioselective variations of the reactions of carbanions in modern synthetic organic chemistry has been fuelled by the use of chiral Lewis acid catalysts from the late 1970's onward and more recently chiral organocatalysts. The overall field of carbanion chemistry and their equivalents is a thriving area of research in modern synthetic organic chemistry.

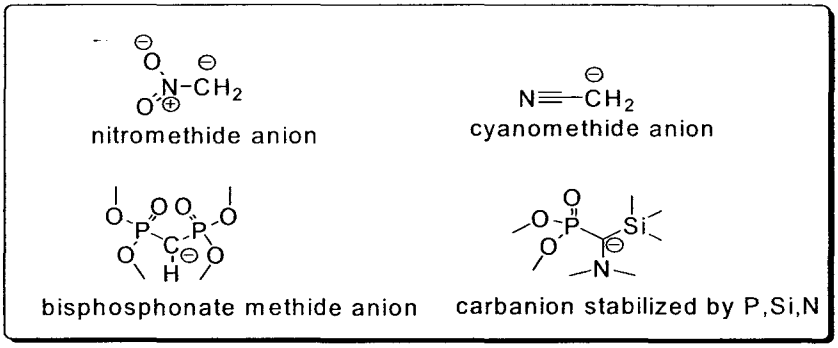
As the name suggests, a carbanion is an anionic species in which a carbon atom bears a formal unit negative charge and the carbanionic center is surrounded by a Lewis octet of electrons. In many cases the lone pair of a carbanion may be delocalized through resonance to a conjugated functional group, as in an enolate carbanion, inductively or even hyperconjugatively to a heteroatom. These effects generally confer stability to the carbanion and differentiate its reactivity in synthetically useful ways. Conceptually, carbanions can be formed by loss of a proton from the corresponding hydrocarbon or

hydrocarbon derivative or by a halogen exchange from the halogen-containing hydrocarbon. Carbanions can be generally classified into two groups. The first group contains carbanions derived from unsubstituted hydrocarbons, Scheme 1. Other than the structure of the carbanion itself, variations on its reactivity are controlled by the nature of the metal and appended ligands.



Scheme 1

The second class includes carbanions in which the negative charge is stabilized by a heteroatom or heteroatom-containing functional group, Scheme 2.



Scheme 2

This second class of finely tunable carbanions and their equivalents are involved in some of the most important strategic carbon-carbon bond forming reactions used in synthetic organic chemistry, a summary of which is compiled in Scheme 3.

The field of heteroatom stabilized carbanion chemistry is rich and diverse. Olefination, alkylation, acylation, and conjugate addition are some of the most important organic reactions where heteroatom stabilized carbanions find extensive use.

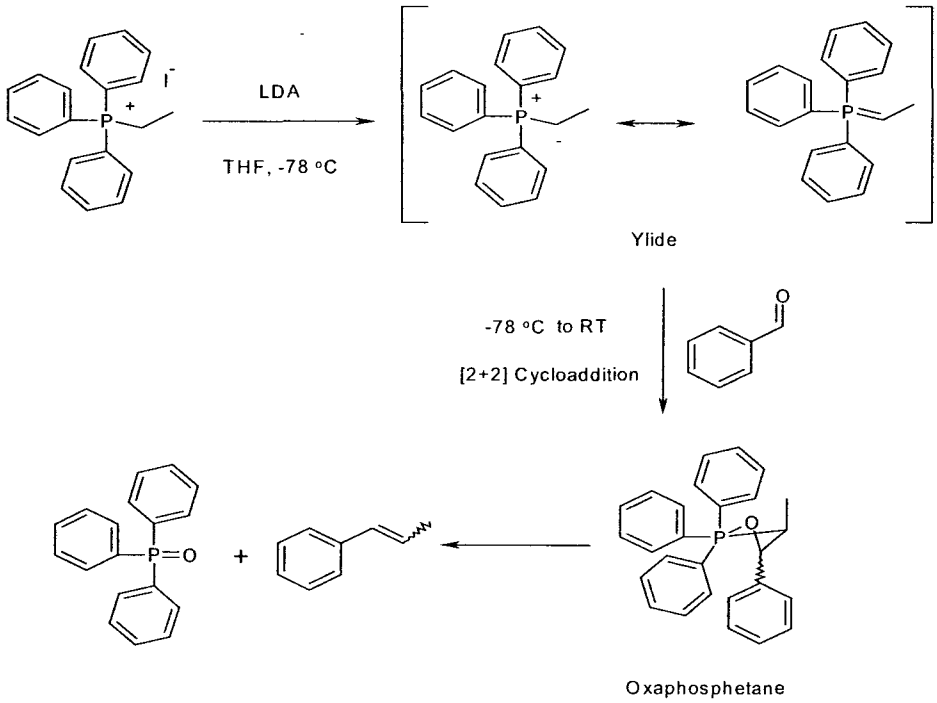
X	Reaction
R_3P^+	Wittig
$R_2P(=O)$	Horner-Wittig
$(RO)_2P(=O)$	Horner-Wadsworth-Emmons
R_3Si	Peterson
$ArS(=O)(=NMe)$	Johnson
$ArSO_2$	classical Julia
$HetSO_2$	modified Julia

Scheme 3

The olefination of carbonyl compounds requires the reaction of a functionalized carbanion or equivalent with a carbonyl compound, as for example in the Peterson and Wittig reactions. The Peterson reaction involves an addition-elimination sequence of an α-silyl (e.g. TMS) carbanion adding to a carbonyl compound occurring in tandem. The anion is usually generated using the lithium-halogen exchange or with a strong base. Various heteroatom-containing groups can stabilize the intermediate anion formed. The Wittig reaction is a special example of the above in which a phosphonium group stabilizes the anion equivalent giving a phosphorus ylide intermediate. This species is electronically neutral but highly dipolar and displays carbanion-like reactivity. The reaction of the ylide with a carbonyl compound is known as the Wittig olefination.

The Wittig and Related Reactions:

The reaction of carbonyl compounds with phosphorus ylides, first described by Wittig and Geissler[2], is the first example and probably the most widely used method for carbonyl olefination employing a heteroatom anion stabilizing group.



Scheme 4. The Wittig reaction

This highly reliable reaction allows for olefination with complete positional selectivity, relatively high chemoselectivity and may be conducted in many cases with reliable and high levels of stereocontrol. A wide variety of phosphorus-based reagents are known to participate in Wittig reactions. Depending upon the exact nature of these species, the Wittig reaction can be divided into three main groups, namely the classical Wittig reaction of phosphonium salt derived ylides, the Horner-Wadsworth-Emmons reaction of phosphonate anions and the Horner-Wittig reaction of anions derived from phosphine oxides.

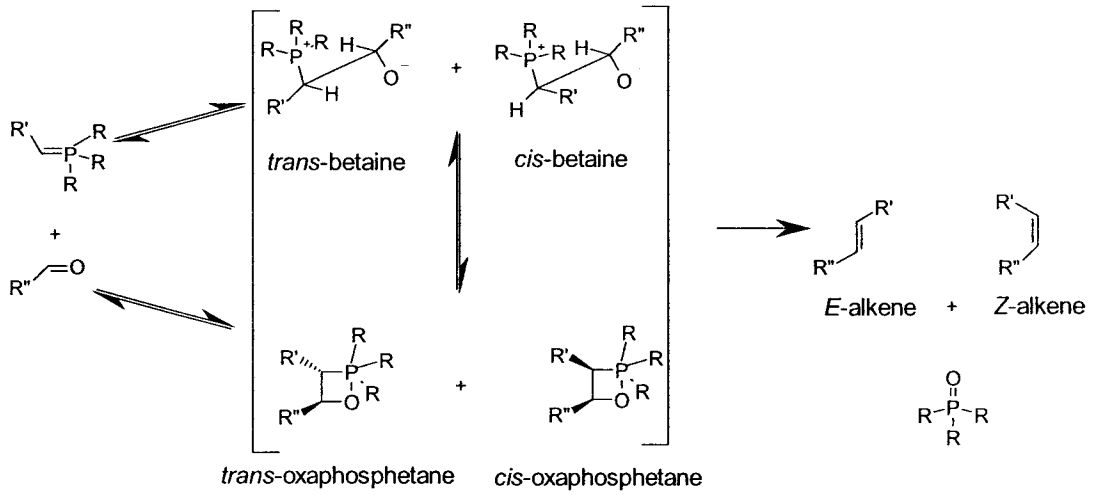
1. The Classical Wittig reaction:[2,3,4,5]

As depicted in Scheme 4, the classical Wittig reaction deals with the reaction of a phosphonium salt-derived ylide with a carbonyl compound to generate the corresponding alkene and phosphine oxide. The reaction is quite general and provides a simple and

straightforward method for the preparation of various alkenes with moderate to good (*E*) to (*Z*) stereocontrol. The reaction generally requires the use strong bases such as LDA or BuLi to generate the ylide from phosphonium salts.

Mechanism and Stereoselectivity:

The mechanism of the Wittig reaction is under still under debate after more than 50 years, however it is generally considered to involve two intermediate species, a zwitterionic betaine and an oxaphosphetane. Wittig first proposed a four-membered cyclic 1,2-oxaphosphetane[2] as early as in 1953. However, later on he came to favor a zwitterionic betaine species as the main intermediate.[3,4] By 1970 this view gained broad acceptance and the Wittig reaction was commonly expressed as a two step process:[5-7,8-12] These steps involved (1) a reversible nucleophilic addition of the phosphorus ylide across a carbonyl carbon to deliver the zwitterionic betaine species and (2) irreversible decomposition of the betaine to give the olefin product and the by-product phosphine oxide. However, later studies using low temperature ^{31}P NMR experiments suggest that this may not be true. Vedejs and co-workers have reported considerable experimental studies on the mechanism of the Wittig reaction and they have supported the mechanism involving the direct oxaphosphetane intermediate.[13,14] Other research groups have also contributed significantly[15-18] by observing oxaphosphetanes at low temperatures. These observations coupled with the lack of experimental evidence for betaines revolutionized the impressions about the Wittig reaction mechanism. The Vedejs group also showed that phosphine oxide elimination was stereospecific from diastereomeric oxaphosphetanes. Nonetheless the initial kinetic formation of betaines is still not ruled out. The currently accepted mechanism of the Wittig reaction is shown in the following scheme.



Scheme 5: The mechanism of the Wittig reaction

Since elimination from the oxaphosphetane is stereospecific, the stereoelectronics of the process involved in formation of the betaine or directly (as shown) the oxaphosphetane governs the stereoselectivity of the Wittig olefination. Under kinetic conditions the (*Z*)-alkene tends to be the major product from non-stabilized (R'= alkyl group) ylides whereas under thermodynamic conditions the (*E*)-alkene tends to be the predominant product. A number of factors determine whether a Wittig reaction is under thermodynamic or kinetic control. The actual structural sub-types of ylide used and the reaction temperature are two most important and readily controllable factors that impact the stereoselectivity of Wittig reaction.

Nature of the Ylide and Carbonyl Compound:

Non-stabilized ylides posses an anion destabilizing or electron releasing group such as a simple alkyl chain. Nonstabilized ylides derived from triarylphosphonium salts tends to give very high (*Z*)-selectivity for the olefination because these reactions are under kinetic control. Vedejs has developed a model involving a four-centered early transition state. He

proposed that, the ylidic carbon attacks the carbonyl group with the C=O axis skewed with respect to the C=P axis[13] as shown below.

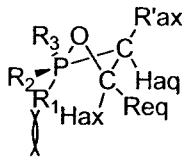


Figure 1

The substituents on the pentacoordinate phosphorus of the oxaphosphetane define a critical steric environment. The substituents on the newly formed stereogenic carbon centers of this skewed oxaphosphetane adopt a geometry involving least steric congestion to each other and to the substituents on the phosphorus atom. This model relies on a subtle balance of 1,3 and 1,2 steric interactions of the substituents of the four-centered oxaphosphetane ring.

Generally, (*Z*)-stereoselectivities in excess of 90% has been experienced for Wittig reactions of nonstabilized ylides with carbonyl compounds. However, replacement of aryl groups on phosphorus with various alkyl groups such as, *t*-Bu, cyclohexyl, and butyl drastically diminishes the (*Z*)-selectivity under kinetic conditions.[14,19,20] It is still difficult to obtain aliphatic (*E*)-olefins with high sterecontrol from the reaction of alkyl-substituted ylides with aldehydes. This is still one of the outstanding problems of current Wittig methodology. Recently McNulty and co-workers have shown an interesting alkoxide effect[21] that mediated high (*E*)-stereoselectivity in nonstablized Wittig reactions with aliphatic aldehydes. Based on this observation, it can be said that cis to trans isomerisation of oxaphosphetane intermediates is possible under certain conditions and this process may involve a betaine intermediate.

Stabilized ylides are those that posses α-electron-withdrawing groups such as, $CO_2C_2H_5$, $COCH_3$, CN, $P(O)O_2CH_3$, SO_2Ph etc. These ylides are more stable and tend to provide high (*E*)-stereoselectivity for the olefination because these reactions are under thermodynamic control.

Semi-stabilized ylides posses phenyl, vinyl or halogens as anion stabilizing groups. These ylides are much more reactive than the stabilized ylide counterparts and their Wittig reactions tend to give very poor stereoselectivity.

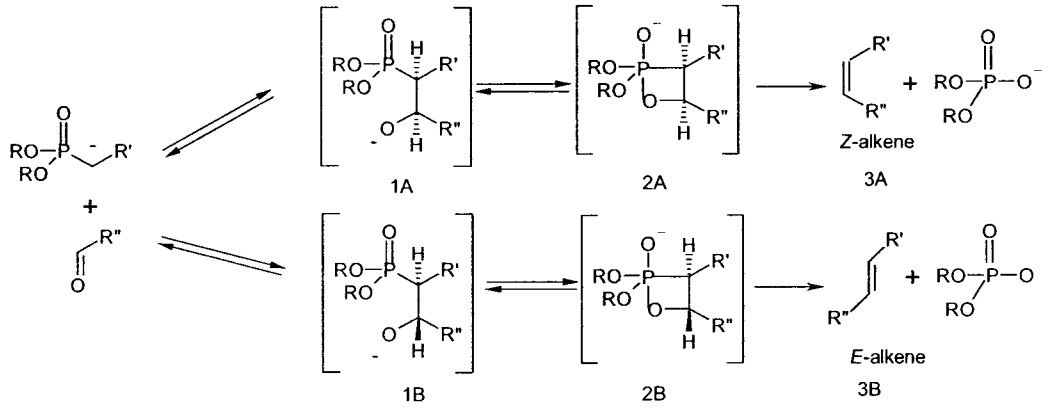
Semi-stabilized and stabilized ylides have been the subject of various kinetic and mechanistic studies.[6,22-26] Based on kinetic studies it can be said that the rate-limiting step is initial condensation of phosphorus ylide and carbonyl, with any intermediates such as oxaphosphetanes or betaines decomposing to olefins too rapidly for their detection.

The Wittig reactions of semi-stabilized ylides derived from triphenylbenzylidenyl or triphenyl allyllidenyl ylides with aldehydes generally results in low configurational stereocontrol. This is quite disappointing since many useful functionalized stilbene, diene and more conjugated systems with definitive stereochemistry are of interest from the fine chemicals, pharmaceutical and materials viewpoints. The inability of the Wittig reaction to provide these olefins with high stereocontrol is a second limitation on current methodology.

2. Horner-Wadsworth-Emmons (HWE) Reaction:[27,28]

The Horner-Wadsworth-Emmons (HWE) reaction deals with the olefination reaction of phosphonate-stabilized anions with a carbonyl partner. Phosphonate stabilized anions react in a similar fashion to the classical Wittig stabilized ylides and one can perform olefination reactions even with hindered ketones. Another advantage of the HWE

reaction is that the byproduct is water soluble and hence readily separated from the desired product. This situation highlights a third limitation of the current Wittig olefination methodology not mentioned above. It is often difficult to remove the triphenylphosphine oxide side-product that is formed, particularly on a large scale and in cases where high purity olefins are required, purification can be tedious.



Scheme 6: The HWE reaction (R'=CO_2Me etc)

Mechanism and Stereoselectivity:

The commonly accepted mechanism of the HWE reaction is shown in Scheme 6. Here, the phosphonate-stabilized anion condenses with the aldehyde to generate the oxyanion intermediate **1** under reversible conditions. The oxyanion intermediate then forms the 4 centered ring intermediate **2** analogous to the oxaphosphetane in the case of Wittig reaction. Rapid decomposition of **2** leads to the formation of alkenes **3**.

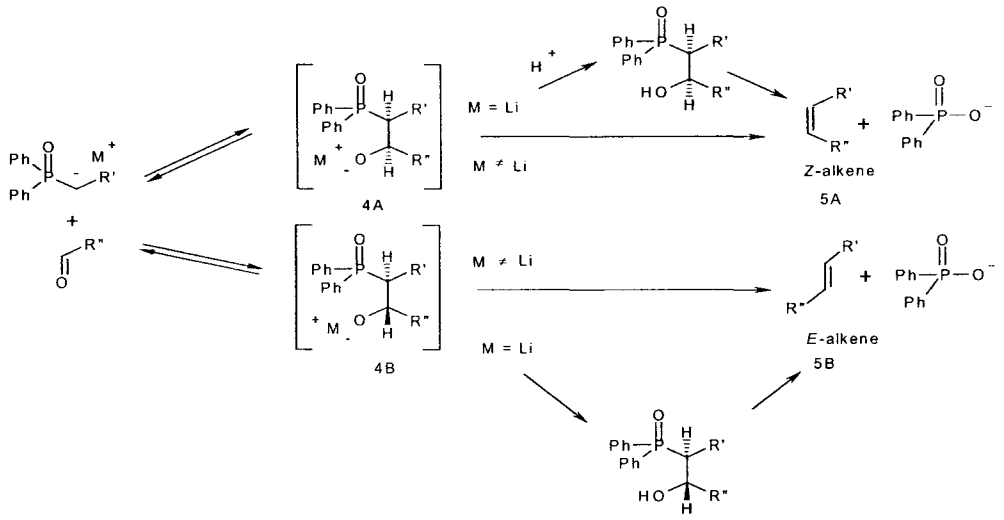
The stereochemistry of the alkene formation depends upon the nature of the phosphonate used. In general, bulky substituents at both the phosphorus and the carbon next to the carbanion favor the formation of (*E*)-alkene. In the case of **2B**, there is less steric crowding as compared to **2A.** As a result olefination takes place mostly from the intermediate **2B** thereby generating (*E*)-alkenes. For (*Z*)-selectivity in HWE reaction, one

needs to use the Still-Gennari's condition[30]. In this case, the use of a (2,2,2-trifluoroethyl) phosphonate increases the rate of elimination from the adduct **2A** (Scheme 6).

3. Horner-Wittig (HW) Reaction:[28,29,31]

Horner-Wittig reaction employs a phosphonate-stabilized anion during the olefination process. Like the HWE reaction, the HW reaction also generates water-soluble phosphinate byproduct and hence this is easily removed from the alkene product. The use of lithium bases has allowed the intermediate β-hydroxy-phosphine oxide diastereomers to be isolated and separated. Each diastereomer can then be treated with a base to generate the corresponding olefin in high geometrical purity.

Mechanism and Stereoselectivity:



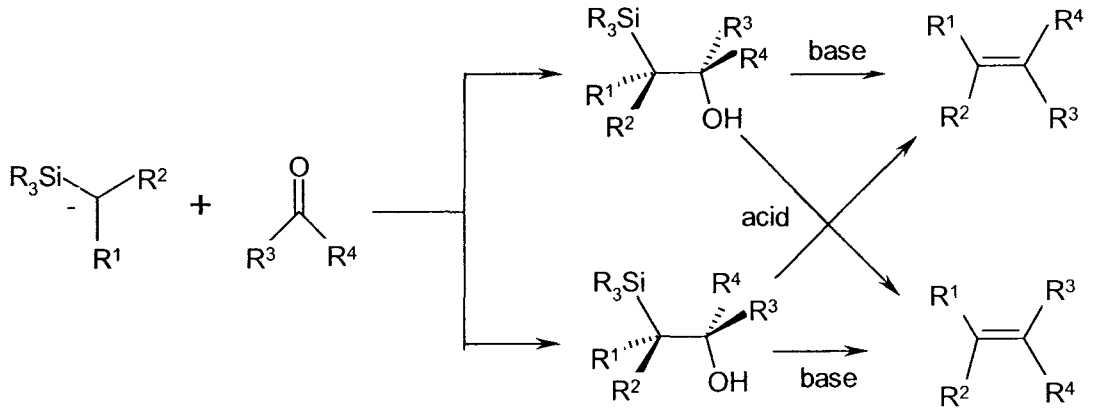
Scheme 7: The HW reaction

The use of a lithium-containing base divides the HW reaction into two discrete steps: 1) addition of a lithiated phosphine oxide to a carbonyl group to generate β-hydroxy-phosphine oxide and 2) the elimination of a phosphinic acid to afford an olefin as shown in Scheme 7.[31] However, in the case of the use of non-lithiated base and a stabilizing R'

group, the reaction produces the olefin directly. Under these conditions, the HW reaction of the phosponate stabilized carbanion with a carbonyl compound to give **4A** and **4B** is reversible. The (*E*)-olefin is formed preferentially since the elimination step is much faster from the diastereomer **4B**.

4.The Peterson Reaction:[32]

The Peterson reaction is the silicon version of the Wittig reaction. D. J. Peterson developed this process in 1968. In this process, an α-silyl carbanion reacts with a carbonyl compound to give an alkene as shown in the following Scheme 8. The intermediate β-hydroxysilanes can also be isolated and separated in some cases. Subsequent elimination produces the olefin from the β-hydroxysilane in a process referred to as "Peterson elimination".



Scheme 8: The Peterson Reaction

The Peterson reaction often gives high stereoselectivity and sufficiently high reactivity to allow reactions with ketones, aldehydes, or other carbonyls. By controlling the reaction conditions, high stereoselectivity can be obtained in the Peterson reaction. The by-product silanol is volatile and can be removed easily from the olefin product(s). In most cases, the silicon-stabilized carbanion is actually the unsubstituted methylenyl-derivative

(Scheme 8, $R^1=R^2=H$) and so the reaction produces terminal olefins or exocyclic double bonds from the reaction with aldehydes and ketones respectively. Examples of the reaction of functionalized version of the Peterson reaction are rare.

In summary, the Wittig reaction is a powerful strategic carbon-carbon bond forming reaction of wide applicability. Despite this, current methodological limitations exist in connection with the stereoselective synthesis of aliphatic (*E*)-olefins from non-stabilized ylides and aliphatic aldehydes as well as from the reaction of semi-stabilized ylides (from allyl or benzyl halides) with aldehydes. In addition, the removal of triphenylphosphine oxide remains a ubiquitous issue in most current applications of the Wittig reaction. We also note that there are still fundamental controversies with respect to the involvement of betaines versus oxaphosphetane intermediates during initial stages of the Wittig reaction. Extension of the Peterson reaction to other functionalized versions also appears to be an area worthy of further exploration. The overall goals of the present work were to investigate the use of trialkylphosphines and functionalized silyl derivatives with a view to addressing some of these methodological limitations and more fundamental concerns. A secondary objective is to allow access to a variety of useful products in a stereocontrolled fashion for future applications in areas including pharmaceutical, fine chemicals and materials-related fields.

References:

1. Buncel, E.; Dust, J. D. *Carbanion Chemistry;* Oxford University Press: New York, **2003**.
2. Wittig, G.; Geissler, G. *Liebigs Ann.* **1953**, 44-57.
3. Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954**, 97, 1318-1330.

4. Wittig, G.; Haag, W. *Chem. Ber.* **1955**, 88, 1654-1666.

5. Trippett, S. *Q. Rev., Chem. Soc.* **1963**, 17, 406-440.

6. Maercker, A. *Org. React.* **1965**, 270-490.

7. Johnson, A. W. *Ylide Chemistry*; Academic Press: New York, **1966**.

8. Schlosser, M.; Christmann, K. F. *Liebigs Ann. Chem.* **1967**, 708, 1-35.

9. Jones, M. E.; Trippett, S. *J. Chem. Soc. C* **1966**, 1090-1094.

10. Lowe, P. A. *Chem. Ind. (London)* **1970**, 1070-1079.

11. Wittig, G.; Weigmann, H.-D.; Schlosser, M. *Chem. Ber.* **1961**, 94, 676-689.

12. Schneider, W. P. *Chem. Commun.* **1969**, 785-786.

13. Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, 103, 2823-2831.

14. Vedejs, E.; Marth, C.; Ruggeri, R, *J. Am. Chem. Soc.* **1988**, 110, 3940-3948.

15. (a) Birum, G. H.; Matthews, C. N. *Chem Commun.* **1967**, 137-138. (b) Kolodyazhnyi, O. I. *Tetrahedron Lett.* **1985**, 26, 439-442. (c) Kolodyazhnyi, O. I. *Tetrahedron Lett.* **1988**, 29, 3663-3666.

16. Ramirez, F.; Smith, C. P.; Pilot, J. F. *J. Am. Chem. Soc.* **1968**, 90, 6726-6732.

17. Ramirez, F.; Loewengart, G. V.; Tsolis, E. A.; Tasaka, K. *J. Am. Chem. Soc.* **1972**, 94, 3531-3536.

18. Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, 107, 217-226.

19. Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R., Jr. *J. Am. Chem. Soc.* **1985**, 107, 1068-1070.

20. Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R., Jr.; Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc.* **1986**, 108, 7664-7678.

21. McNulty, J.; Keskar, K. *Tetrahedron Lett.* **2008**, 49,7054-7057.

22. Vedejs, E.; Fleck, T.; Hara, S. *J. Org. Chem.* **1987**, 52, 4637-4639.

23. Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, 95, 822-825.

24. McEwen, W. E.; Beaver, B. D. *Phosphorus Sulfur* **1985**, 24, 259-271.

25. Speziale, A. J.; Bissing, D. E. *J. Am. Chem. Soc.* **1963**, 85, 3878-3884.

26. (a) Johnson, A. W.; Kyllingstad, V. L. *J. Org. Chem.* **1966**, 31, 334-336. (b) Allen, D. W.; Ward, H. Z. *Naturforsch.* **1980**, 35b, 754-757. (c) Giese, B.; Schoch, J.; Ruchardt, C. *Chem. Ber.* **1978**, 111, 1395-1403. (d) Donxia, L.; Dexian, W.; Yaozhong, L.; Huaming, Z. *Tetrahedron* **1986**, 42, 4161-4167. (e) Isaacs, N. S.; Abed, O. H. *Tetrahedron Lett.* **1986**, 27, 995-996. (f) Johnson, A. W.; LaCount, R. B. *Tetrahedron Lett.* **1986**, 27, 1541-1544. (g) Mylona, A.; Nikokavouras, J.; Takakia, I. M. *J. Org. Chem.* **1988**, 53, 3838-3841.

27. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, 89, 863-490.

28. Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, 21, 1-157.

29. Walker, B. J. in *Organophosphorus Reagents in Organic Synthesis*, Academic press, London, **1979**, 155-205.

30. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405-4408.

31. Horner, L.; Hoffman, H. G. *Chem. Ber.* **1959**, 92, 2499-2505.

32. Peterson, D. J. *J. Org. Chem.* **1968**, 33, 780-784.

Chapter I

An improved synthesis of alpha-phosphonoenamines based on a modified Peterson olefination

Introduction:

Approaches toward the synthesis of α-amino phosphonates 1 (Figure 1) and derivatives,[1,2] have been intensely investigated over the last few decades with applications as peptide-mimics due to their homology with the corresponding α–amino acids. Not surprisingly, these compounds are inhibitors of a range of proteolytic enzymes and derivatives have now been shown to exhibit a wide range of biological properties,[1] including antibacterial activity.[3] On the other hand, the related α,β-unsaturated-α-phosphonoenamines such as 3 (Figure 1) have received considerably less synthetic attention,[4,5] although some have also been shown to possess biological activity.[6]

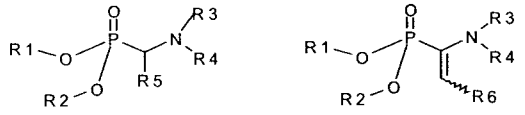
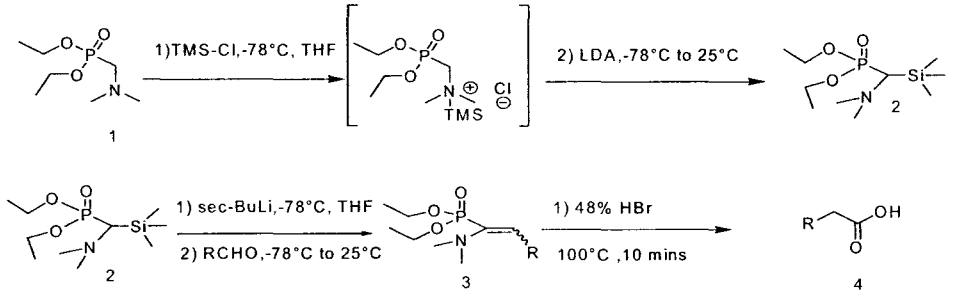


Figure 1. General α-aminophosphonate **1** and α-phosphonoenamine **3** structures.

The syntheses of these latter compounds has been achieved mainly from α–aminodiphosphonates[4] using carbanion chemistry, however these procedures provide low (29-47%) to moderate (average 55%) yield of the desired α- phosphonoenamine intermediate as (*E*)/(*Z*) mixtures, in part due to the sensitivity of the enamine functionality. The lack of a reliable, high yielding synthesis of α-phosphonoenamines **3** has hindered application and development of these derivatives. In a singular example, Gross and co-workers reported the hydrolysis of these intermediates to give homologated

carboxylic acids.[4d] This appears to be a potentially valuable synthetic interconversion (aldehyde to homologated acid) although to our knowledge it has never been applied due to the difficulty in accessing the necessary phosphonoenamine intermediate. The dense functionality found in α-phosphonoenamines **3** in conjunction with the commercially available α–N,N-dimethylamino-phosphononate **1**[7] stimulated our interest in developing the aldol-type reaction shown (Scheme 1) as a route to phosphonoenamines. Here we report that while the direct reaction of enolate derivatives of **1** with aldehydes is problematic, the trimethylsilyl derivative of this compound readily enters into such reactions with both aromatic and aliphatic aldehydes in Peterson-fashion to yield α–phosphonoenamines in high yield. These intermediates undergo ready hydrolysis in aqueous HBr extending the carbonyl-homologation strategy (aldehyde to homologated carboxylic acid) to a range of aromatic and aliphatic carboxylic acids.[4d]



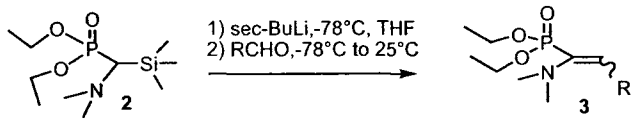
Scheme 1

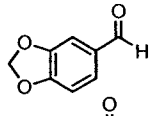
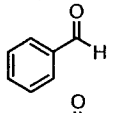
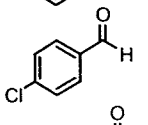
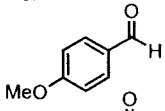
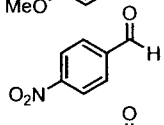
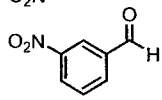
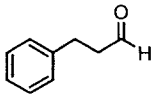
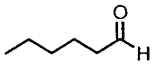
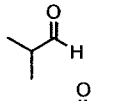
Results & Discussion:

We prepared the α–trimethylsilyl derivative **2** (Scheme 1) employing a silylation strategy first described by Padwa *et al* in the silylation of cyanoamines.[9] In the present case, rapid N-silylation of **1** with trimethylsilylchloride gave the trimethylsilyl ammonium salt. Deprotonation with LDA promoted the desired N to C migration of the trimethylsilyl

group most likely *via* a nitrogen ylide intermediate. The trimethylsilyl intermediate **2** proved to be stable to silica gel and could be stored under argon for several days without decomposition. The intermediate was however readily hydrolyzed back to the starting aminophosphonate **1** when treated with aqueous acid. Formation of the α–silyl carbanion from the above intermediate **2** using *s*-BuLi in THF (-78 °C) and addition of piperonal, as outlined in Scheme 1, to our delight led to the formation of the corresponding phosphonoenamine **3a** with 95% conversion and 87% isolated yield. Although the precise mechanism of the Peterson reaction is still unclear (so-called betaine versus oxasiletanide intermediates) [8] we were relieved to find that the intermediate, selected the Peterson elimination pathway over the Horner-Emmons route. Vinylsilanes are also possible products from this reaction and this "challenge" clearly demonstrates the prominence of the Peterson route through silicon-oxygen bond formation, reactivity also observed with simple α–silylphosphonates.[8] The scope of the reaction was investigated with a range of aromatic and aliphatic aldehydes the results of which are summarized in Table 1. Conversions are high in all cases with isolated yields being only slightly lower. Under these conditions of kinetic control, aromatic aldehydes provided a mixture of (*E*)/(*Z*) olefins that rapidly isomerize to give exclusively the thermodynamically more stable (*E*)-isomers. No significant electronic effect was observed with both electron rich and electron poor derivatives reacting equally well (entries 1 to 6). With the exception of dihydrocinnamaldehyde (entry 7), for which a single stereoisomer was obtained, adducts from aliphatic aldehydes did not isomerize and a mixture of the seperable configurational isomers was obtained (entries 8 and 9). The heteroaryl aldehyde 2-furfural also yielded its corresponding adduct efficiently (entry 10). Although the reactivity of α-

phosphonoenamines remains largely unexplored (*vide supra*) the obvious synthetic potential of the homologation strategy prompted our further interest.



Entry	RCHO	conversion (%) **3**	isolated yield of **3** (%)[a]	E:Z[b]
1	 (2a)	>95 **3a**	87	100:0
2	 (2b)	>90 **3b**	67	100:0
3	 (2c)	>94 **3c**	80	100:0
4	 (2d)	>95 **3d**	85	100:0
5	 (2e)	>95 **3e**	82	100:0
6	 (2f)	>95 **3f**	80	100:0
7	 (2g)	>90 **3g**	75	100:0
8	(2h)	>90 **3h**	70	60:40
9	 (2i)	>90 **3i**	70	65:35
10	 (2j)	>95 **3j**	75	100:0

[a] Isolated yield of thephosphonoenamine **3** after chromatographic purification. [b]The (*Z*)- isomer derived from aromatic aldehydes fully converts to the (*E*)- isomer, see text. In the case of aliphatic aldehydes, both configurational isomers were separated.

Table 1

The use of boiling hydrochloric acid was reported to give carboxylic acids through initial enamine hydrolysis and cleavage of the derived α–ketophosphonate intermediate.[4d] Three

examples of this reaction were reported by Gross and Costisella; [4d] however it does not appear to have been applied and the synthetic potential of this protocol is largely unrecognized due to the prior difficulty in accessing intermediates **3**. In our hands, treatment of the piperonal adduct **3a** with 48% HBr and warming led to rapid hydrolysis and isolation of the homologous acid in 90% yield (Table 2, entry 1). The reaction proved to be general for both electron rich and electron deficient aryl derivatives (Table 2, entries 2 to 5) with high yields of carboxylic acid being obtained in all cases. Lastly, the hexanal derived α–phosphonoenamine **3f** was readily hydrolyzed to heptanoic acid (Table 2, entry 6) extending the scope to aliphatic derivatives for the first time.

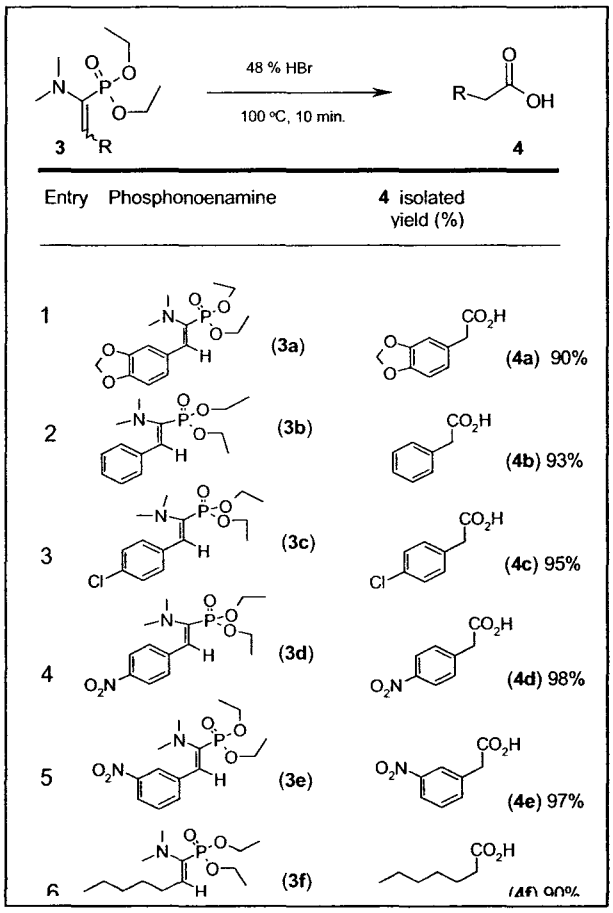


Table 2

While several well-known carbonyl homologation strategies are employed in synthetic chemistry, most involve several steps in order to extend an aldehyde or ketone to the homologated aldehyde. The present two-step method appears to be potentially useful. In the overall process; an aldehyde is converted into the homologous carboxylic acid **4** *via* the intermediacy of **3**. Few methods have been reported to effect this precise transformation (aldehyde to homologated acid).[10] Furthermore, the method allows efficient conversion of common aldehydes to phenylacetic acid and substituted derivatives which are valuable industrial intermediates in the production of pharmaceuticals, cosmetics and fragrances.[11]

Conclusion:

In conclusion, the scope of the Peterson route to α-phosphonoenamines **3** described herein appears to be wide and an expanded range of derivatives are now available using this methodology. While certain of these derivatives have been prepared using the Horner-Emmons olefination reaction of diphosphonates,[4] the greater efficiency of the Peterson olefination likely derives from the higher oxygenophilicity of silicon versus phosphorus,[8] enabling milder reaction conditions and minimizing the decomposition of labile α-phosphonoenamines **3**. Subsequent hydrolysis of these intermediates in warm hydrobromic acid appears to be a general method for the overall conversion of both aromatic and aliphatic aldehydes into the homologous carboxylic acid derivatives.

References:

1. For some recent examples see: (a) Wu, J.; Sun, X.; Xia, H-G. *Green Chem.* **2006**, 8, 365-367. (b) Palacios, F.; Ochoa de Retana, A.M.; Alonso, J.M. *J. Org. Chem.* **2005**, 70, 8895-8901. (c) Azizi, N.; Saidi, M.R. *Tetrahedron* **2003**, 59, 5329-5332. (d)

Steere, J.A.; Sampson, P.B.; Honek, J.F. *Bioorg. & Med Chem. Lett.* **2001**, 12, 457-460. (e) Kafarski, P.; Lejczak, B. *Curr. Med. Chem. Anti Cancer Agents* **2001**, 1, 301-312.

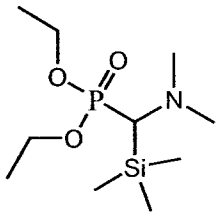
2. Li, S.; Whitehead, J.K.; Hammer, R.P. *J. Org. Chem.* **2007**, 72, 3116-3118.
3. Pratt, R.F. *Science*, **1989**, 246, 917-919.
4. (a) Qian, D.Q.; Shi, D.S.; Cao, R.Z.; Liu, L.Z. *Heteroatom Chem.* **1999**, 10, 271-276. (b) Costisella, B.; Keitel, I.; Gross, H. *Tetrahedron* **1981**, 37, 1227-1232. (c) Ahlbrecht, H.; Farnung, W. *Synthesis* **1977**, 336-338. (d) Gross, H.; Costisella, B. *Angew. Chem. Int. Ed.* **1968**, 7, 391-392.
5. Schindler, N.; Ploger, W. *Chem. Ber.* **1971**, 104, 2021-2022.
6. Zumstein, F.; Klingseisen, F. *Ger. Offen.* **1990**, DE 4029444 A1.
7. This intermediate is available from Cytec Industries.
8. van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, 31, 195-200. Ager, D. J. *Org. React.* **1990**, 38, 1.
9. Padwa, A.; Eisenbarth, P.; Venkatramanan, M. K.; Wong, G. S. K. *J. Org. Chem.* **1987**, 52, 2427-2432.
10. Zhou, G.B.; Zhang, P.F.; Pan, Y.J. *Tetrahedron* **2005**, 61, 5671-5677.
11. Kohlpaintner, C.W.; Beller, M. *J. Mol. Cat. A: Chem.* **1997**, 116, 259-267.

Experimental:

General Information:

Reactions were carried out under an Argon atmosphere in oven-dried glassware. Toluene and THF were distilled from sodium metal with benzophenone indicator. Diethyl N'N-dimethylamino-phosphonate was obtained from Cytec, all other fine chemicals were obtained from Aldrich. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV and HRMS (CI) were performed with a Micromass Q-Tof Ultima spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 200 or AV 700 spectrometer in $CDCl_3$ with TMS as internal standard, chemical shifts (δ) are reported in ppm downfield of TMS and coupling constants (J) are expressed in Hz.

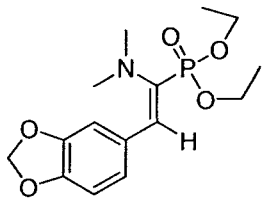
Diethyl 1-dimethylamino-1-trimethylsilylmethanophosphonate (2):



Into a 20 mL flame-dried round bottom flask, containing a magnetic stirring bar, was added diethyl-2-N,N-dimethylaminomethanophosphonate **1** (500μL, 4.13 mmol) under argon. To this was added dry THF (8.26 mL). The contents were cooled to -78 °C and stirred for 15 min. whereupon TMS-Cl (550 μL, 4.35 mmol) was added to the reaction flask over 5 min. Upon stirring for 30 min, a solution of LDA (2.5 mL, 5.0 mmol, 2 M, THF) was added slowly to the reaction flask maintained at –78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 6 h. The resulting mixture was concentrated to remove solvent. Water was added

(10 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product, R_f = 0.32 (EtOAc, pink-red to ninhydrin), was purified by silica gel column chromatography (EtOAc). Adding 5 drops of triethylamine into the initial silica gel slurry neutralized the silica gel. The title compound **2**, 882.2 mg (80%) was isolated as a brown oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.14 (s, 9H), 1.33 (t, J_{HH} = 6.4 Hz, 6H), 2.38 (d, J_{PH} = 22.2 Hz, 1H), 2.47 (s, 6H), 4.07 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ -0.6 (d, J = 2.5 Hz), 16.5 (dd, J_{PC} = 6.30 Hz, 2.5 Hz), 45.5 (d, J_{PC} = 3.8 Hz), 55.3 (d, J_{PC} = 112.5 Hz), 60.7 (t, J_{PC} = 7.8 Hz); ^{31}P-NMR (80 MHz, $CDCl_3$): δ 30.8; HRMS $(M)^+$ calcd. for $C_{10}H_{26}N_1O_3SiP$: 267.1421, found: 267.1420.

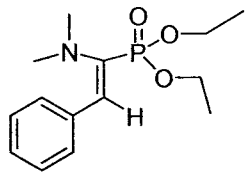
(*E*)-Diethyl-1-dimethylamino-2-(3',4'-methylenedioxy)phenyl-vinylphosphonate (3a):



Into a flame dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (74 mg, 0.278 mmol). The flask was sealed under argon whereupon dry THF (556 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C at which time *s*-BuLi (239 μL, 1.4 M stock) was added slowly. After 40 min, a 0.5 M solution (in THF) of piperonal (50 mg, 0.33 mmol) was added slowly to the reaction flask at –78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two spots were visible on tlc (UV visible and pink-red with ninhydrin). The product was separated using column chromatography

(ethyl acetate as eluant) to give **3a**, 87 % (79.1 mg). *Rf.* (AcOEt): 0.36. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.35 (t, J_{HH} = 7.0 Hz, 6H), 2.65 (d, J_{PH} = 2.0 Hz, 6H), 4.13 (m, 4H), 5.94 (s, 2H), 6.67 (d, J_{PH} = 14.9 Hz, 1H), 6.75 (d, J_{HH} = 7.8 Hz, 1H), 7.45 (s, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.4 (d, J_{PC} = 6.8 Hz), 43.1 (d, J_{PC} = 2.3 Hz), 61.6 (d, J_{PC} = 5.6 Hz), 101.1, 107.9, 109.3, 125.0, 129.4 (d, J_{PC} = 15.7 Hz), 130.9 (d, J_{PC} = 31.8 Hz), 137.8 (d, J_{PC} = 182.1 Hz), 147.3, 147.5; ^{31}P-NMR (80 MHz, $CDCl_3$): δ 18.0; HRMS $(M)^+$ calculated for $C_{15}H_{22}N_1O_5P_1$ 327.1237, found 327.1236.

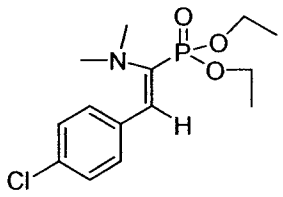
(*E*)-Diethyl-1-dimethylamino-2-phenylvinylphosphonate (3b):



Into a flame dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (109.5 mg, 0.41 mmol). The flask was sealed under argon whereupon dry THF (820 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C. 352 μL *s*-BuLi (1.4 M stock) solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of benzaldehyde (52 mg, 0.49 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3b**, 67% (77.7 mg). *Rf.* (AcOEt): 0.42. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.37 (t, J_{HH} = 7.4 Hz, 6H), 2.69 (d, J_{PH} = 1.7 Hz, 6H), 4.15 (m, 4H), 6.7 (d, J_{PH} = 15.4 Hz, 1H), 7.29 (m, 3H), 7.57 (d, J_{HH} = 8.9 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.4 (d, J_{PC} = 6.4 Hz), 43.1, 61.8 (d, J_{PC} = 5.5 Hz), 127.4 (d,

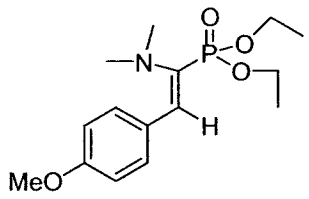
J_{PC} = 32.1 Hz), 127.6, 129.7, 135.3 (d, J_{PC} = 14.2 Hz), 139.2 (d, J_{PC} = 181.6 Hz); ^{31}P-NMR (80 MHz, $CDCl_3$): δ 17.5; HRMS $(M)^+$ calculated for $C_{14}H_{22}N_1O_3P_1$: 283.1324, found 283.1337.

(*E*)-Diethyl-1-dimethylamino-2-(4'-chlorophenyl)-vinylphosphonate (3c):



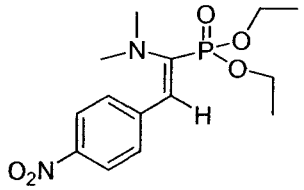
Into a flame dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (38 mg, 0.14 mmol). The flask was sealed under argon whereupon dry THF (300 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C. 150 μL *s*-BuLi (1.4 M stock) solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of 4-chlorobenzaldehyde (24 mg, 0.17 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78°C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3c**, 80 % (36.1 mg). *Rf.* (AcOEt): 0.34. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.35 (t, J_{HH} = 7.3 Hz, 6H), 2.67 (d, J_{PH} = 0.9 Hz, 6H), 4.14 (m, 4H), 6.61 (d, J_{PH} = 14.5 Hz, 1H), 7.27 (d, J_{HH} = 13.2 Hz, 2H), 7.5 (d, J_{HH} = 13.2 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.4 (d, J_{PC} = 5.7 Hz), 43.2, 61.9 (d, J_{PC} = 5.5 Hz), 126.2 (d, J_{PC} = 35.7 Hz), 128.3, 130.8, 133.1, 134.1 (d, J_{PC} = 19.7 Hz), 140.1 (d, J_{PC} = 178.6 Hz); ^{31}P-NMR (80 MHz, $CDCl_3$): δ 17.2; HRMS $(M)^+$ calculated for $C_{14}H_{21}N_1O_3C_{l1}P_1$: 317.0948, found 317.0953.

(*E*)-Diethyl-1-dimethylamino-2-(4'-methoxyphenyl)vinylphosphonate (3d):



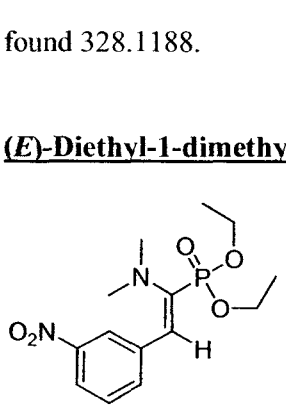
Into a flame dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (91.6 mg, 0.34 mmol). The flask was sealed under argon whereupon dry THF (686 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C. 294 μL *s*-BuLi (1.4 M stock) solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of 4-methoxybenzaldehyde (50 μL, 0.41 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3d**, 85%. *Rf.* (AcOEt): 0.36. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.36 (t, J_{HH} = 7.2 Hz, 6H), 2.7 (d, J_{PH} = 1.2 Hz, 6H), 3.72 (s, 3H), 4.14 (m, 4H), 6.72 (d, J_{PH} = 14.2 Hz, 1H), 6.86 (d, J_{HH} = 9.1 Hz, 2H), 7.65 (d, J_{HH} = 8.7 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.5 (d, J_{PC} = 5.6 Hz), 43.1, 55.2, 61.6 (d, J_{PC} = 5.5 Hz), 113.6, 128.1 (d, J_{PC} = 18.2 Hz), 130.3 (d, J_{PC} = 34.2 Hz), 131.5, 137.3 (d, J_{PC} = 179.1 Hz) 159.3; ^{31}P-NMR (80 MHz, $CDCl_3$): δ 18.3; HRMS $(M)^+$ calculated for $C_{15}H_{25}N_1O_4P_1$: 314.1513, found 314.1521.

(*E*)-Diethyl-1-dimethylamino-2-(4'-nitrophenyl)vinylphosphonate (3e):



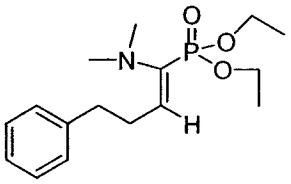
Into a flame dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (74 mg, 0.28 mmol). The flask was sealed under argon whereupon dry THF (555 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C. 238 μL *s*-BuLi (1.4 M stock) solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of 4-nitrobenzaldehyde (50mg, 0.33 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3e**, 82 % (74.8 mg). *Rf.* (AcOEt): 0.29. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.37 (t, J_{HH} = 7.7 Hz, 6H), 2.75 (s, 6H), 4.14 (m, 4H), 6.52 (d, J_{PH} = 14.9 Hz, 1H), 7.49 (d, J_{HH} = 9.3 Hz, 2H), 8.15 (d, J_{HH} = 9.3 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.4 (d, J_{PC} = 5.4 Hz), 43.6, 62.3 (d, J_{PC} = 5.5 Hz), 119.1 (d, J_{PC} = 34.6 Hz), 123.4, 129.3, 142.7(d, J_{PC} = 13.5 Hz), 144.3 (d, J_{PC} = 178.1 Hz), 147.6; ^{31}P-NMR (80 MHz, $CDCl_3$): δ 15.0; HRMS (M^+) calculated for $C_{14}H_{21}N_2O_5P_1$: 328.1188, found 328.1188.

(*E*)-Diethyl-1-dimethylamino-2-(3'-nitrophenyl)vinylphosphonate (3f):



Into a flame dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (91.6 mg, 0.34 mmol). The flask was sealed under argon whereupon dry THF (686 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C. 238 μL *s*-BuLi (1.4 M stock) solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of 3-nitrobenzaldehyde (50 mg, 0.33 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3f**, 80% (73 mg). *Rf.* (AcOEt): 0.28. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.37 (t, J_{HH} = 7.2 Hz, 6H), 2.73 (d, J_{PH} = 1.6 Hz, 6H), 4.17 (m, 4H), 6.61 (d, J_{PH} = 14.9 Hz, 1H), 7.46 (t, J_{HH} = 8.5 Hz, 1H), 7.72 (d, J_{HH} = 6.7 Hz, 1H), 8.03 (d, J_{HH} = 6.7 Hz, 1H), 8.73 (s, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.5 (d, J_{PC} = 5.5 Hz), 43.4, 62.2 (d, J_{PC} = 5.4 Hz), 120.2, 121.4 (d, J_{PC} = 33.2 Hz), 123.5, 128.9, 135.2, 137.4 (d, J_{PC} = 17.2 Hz), 139.2 (d, J_{PC} = 179.4 Hz), 148.4; ^{31}P-NMR (80 MHz, $CDCl_3$): δ 15.9; HRMS $(M)^+$ calculated for $C_{14}H_{22}N_2O_5P_1$: 329.1266, found 314.1266.

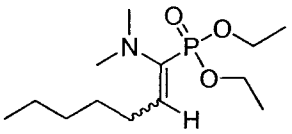
(*E*)-Diethyl-1-dimethylamino-4-phenyl-1-butenylphosphonate (3g):



Into a flame dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (85 mg, 0.32 mmol). The flask was sealed under argon whereupon dry THF (636 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C. 273μL *s*-BuLi (1.4 M stock) solution was added to the reaction flask slowly. After

40 min, a 0.5 M solution (in THF) of hydrocinnamaldehyde (50 μL, 0.38 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature .At the end of the reaction two new spots were seen (UV visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant). The yield of the new product was 75% (74 mg). *Rf.* (AcOEt): 0.4. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J_{HH} = 6.7 Hz, 6H), 2.55 (d, J_{PH} = 2.1 Hz, 6H), 2.67 (m, 4H), 4.02 (m, 4H), 6.12 (dt, J_{PH} = 14.9 Hz, J_{HH} = 7.3 Hz, 1H), 7.22 (m, 5H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.4 (d, J_{PC} = 6.6 Hz), 29.3 (d, J_{PC} = 14.8 Hz), 34.8, 43.8, 61.5 (d, J_{PC} = 7.0 Hz), 126.0, 128.3, 128.4, 138.6 (d, J_{PC} = 31.1 Hz), 140.1 (d, J_{PC} = 179.0 Hz); 141.5; ^{31}P-NMR (80 MHz, $CDCl_3$): δ 17.3; HRMS $(M)^+$ calculated for $C_{16}H_{27}N_1O_3P_1$: 312.1718, found 312.1729.

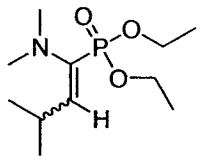
(*E*) and (*Z*)-Diethyl-1-dimethylamino-1-heptenylphosphonate (3h):



Into a flame dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (90.5 mg, 0.34 mmol). The flask was sealed under argon whereupon dry THF (678 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C. 290 μL *s*-BuLi (1.4 M stock) solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of hexanal (50 μL, 0.41 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV visible and pink-red with ninhydrin). The two products were separated using column chromatography (ethyl acetate as eluting solvent). The total yield was 70% (66 mg).

Isolated yield of the *Z* isomer was 40% (26.3 mg) and that of the *E* isomer was 60% (39.7 mg). ***Z*** Isomer: *Rf.* (AcOEt): 0.48. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.87 (t, J_{HH} = 4.5 Hz, 3H), 1.30 (m, 12H), 2.38 (m, 2H), 2.57 (s, 6H), 4.09 (m, 4H), 5.45 (dt, J_{PH} = 41.8 Hz, J_{HH} = 9.9 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.0, 16.3 (d, J_{PC} = 6.0 Hz), 22.2, 28.2, 29.5, 31.5, 43.7 (d, J_{PC} = 5.2 Hz), 61.6 (d, J_{PC} = 5.0 Hz), 128.7 (d, J_{PC} = 28.4 Hz), 141.0 (d, J_{PC} = 190 Hz); ^{31}P-NMR (80 MHz, $CDCl_3$): δ 16.0; HRMS $(M)^+$ calculated for $C_{13}H_{29}N_1O_3P_1$: 278.1885, found 278.1891. ***E*** isomer: *Rf.* (AcOEt): 0.52. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.85 (t, J_{HH} = 6.4 Hz, 3H), 1.30 (m, 12H), 2.23 (m, 2H), 2.58 (s, 6H), 4.06 (m, 4H), 6.11 (dt, J_{PH} = 13.4 Hz, J_{HH} = 6.2 Hz, 1H); ^{13}C -NMR (50 MHz, $CDCl_3$): δ 13.8, 16.4 (d, J_{PC} = 6.7 Hz), 22.4, 27.5 (d, J_{PC} = 14.6 Hz), 28.3 (d, J_{PC} = 2.0 Hz), 31.6, 43.8 (d, J_{PC} = 2.3 Hz), 61.4 (d, J_{PC} = 5.8 Hz), 139.7 (d, J_{PC} = 182.4 Hz), 140.4 (d, J_{PC} = 29.4 Hz); ^{31}P -NMR (80 MHz, $CDCl_3$): δ 17.7; HRMS $(M)^+$ calculated for $C_{13}H_{29}N_1O_3P_1$: 278.1885, found 278.1891.

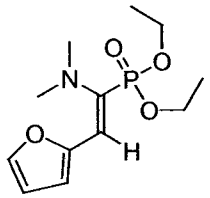
(*E*)- and (*Z*)-Diethyl-1-dimethylamino-3-methyl-1-butenylphosphonate (3i):



Into a flame dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (134.5 mg, 0.50 mmol). The flask was sealed under argon whereupon dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C. 429 μL *s*-BuLi (1.4 M stock) solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of furfuraldehyde (50 μL, 0.60 mmol) was added slowly to the reaction flask at –78 °C. The flask was kept at -78 °C for 2 h and then

slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV visible and pink-red with ninhydrin). The two products were separated using column chromatography (ethyl acetate as eluant). The total yield was 70% (80 mg). Isolated yield of the *Z* isomer was 35% (28 mg) and that of the *E* isomer was 65% (52 mg). ***Z*** isomer: *Rf.* (AcOEt): 0.42. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.95 (t, J_{HH} = 6.5 Hz, 6H), 1.30 (t, J_{HH} = 7.1 Hz, 6H), 2.56 (s, 6H), 3.1 (m, 1H), 4.09 (m, 4H), 5.22 (dd, J_{PH} = 42.2 Hz, J_{HH} = 10.3 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.4 (d, J_{PC} = 6.3 Hz), 23.4, 27.4, 43.8 (d, J_{PC} = 6.9 Hz), 61.6 (d, J_{PC} = 6.3 Hz), 136.0 (d, J_{PC} = 24.7 Hz), 137.2 (d, J_{PC} = 180.5 Hz); ^{31}P-NMR (80 MHz, $CDCl_3$) δ 16.2; HRMS $(M)^+$ calculated for $C_{11}H_{25}N_1O_3P_1$ 250.1565, found 250.1572. ***E*** isomer: *Rf.* (AcOEt): 0.47. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.99 (t, J_{HH} = 7.6 Hz, 6H), 1.33 (t, J_{HH} = 6.9 Hz, 6H), 2.60 (d, J_{PH} = 2.2 Hz, 6H), 2.98 (m, 1H), 4.08 (m, 4H), 6.0 (dd, J_{PH} = 14.2 Hz, J_{HH} = 10.2 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.5 (d, J_{PC} = 6.25 Hz), 22.3, 26.8 (d, J_{PC} = 16.3 Hz), 44.4, 61.7 (d, J_{PC} = 7.3 Hz), 138.0 (d, J_{PC} = 181.5 Hz), 148.3 (d, J_{PC} = 28.9 Hz); ^{31}P-NMR (80 MHz, $CDCl_3$): δ 17.7; HRMS $(M)^+$ calculated for $C_{11}H_{25}N_1O_3P_1$: 250.1565, found 250.1572.

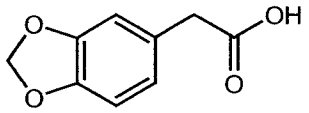
(*E*)-Diethyl-1-dimethylamino-2-(furan-2'-yl)vinylphosphonate (3j):



Into a flame dried flask containing a magnetic stirring bar was weighed the α-silylphosphonate **2** (134.5mg, 0.50 mmol). The flask was sealed under argon whereupon dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at

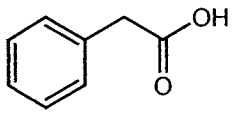
-78 °C. 290 μL *s*-BuLi (1.4 M stock) solution was added to the reaction flask slowly. After 40 min, a 0.5 M solution (in THF) of hexanal (50 μL, 0.41 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature. At the end of the reaction two new spots were seen (UV visible and pink-red with ninhydrin). The product was separated using column chromatography (ethyl acetate as eluant) to give **3j**, 75% (103 mg). *Rf.* (AcOEt): 0.37. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.33 (t, J_{HH} = 7.2 Hz, 6H), 2.72 (d, J_{PH} = 2.0 Hz, 6H), 4.13 (m, 4H), 6.45 (m, 1H), 6.73 (m, 2H), 7.41(s, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 16.5 (d, J_{PC} = 6.9 Hz), 43.2, 61.9 (d, J_{PC} = 5.8 Hz), 112.0 (d, J_{PC} = 15.1 Hz), 112.4, 118.7 (d, J_{PC} = 33.2 Hz), 142.4 (d, J_{PC} = 187.2 Hz), 145.7, 151.0; ^{31}P-NMR (80 MHz, $CDCl_3$): δ 17.7; HRMS $(M)^{+}$ calculated for $C_{12}H_{21}N_1O_4P_1$: 274.1194, found 274.1208.

3,4-Methylenedioxyphenylacetic acid (4a):



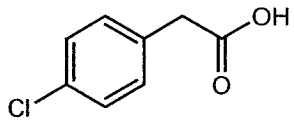
Into a flame dried flask was weighed phosphonoenamine **3a** (50 mg, 0.158 mmol) and 3.0 mL of 48% HBr was added to the flask. The flask was heated with a heat gun for 10 mins. The flask was cooled immediately. Deposits were seen in the reaction flask, which was extracted with diethyl ether (3X15 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield **4a,** 26.8mg, (95%); off-white solid, mp 125-127 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.57 (s, 2H), 5.91 (s, 2H), 6.71-6.81 (m, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 41.4, 107.8, 109.3, 123.2, 127.7, 146.8, 147.9, 177.6. CAS registry number [2861-28-1].

Phenylacetic acid (4b):



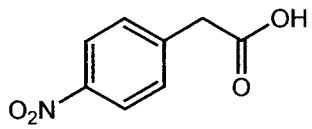
Into a flame dried flask was weighed phosphonoenamine **3b** (50 mg, 0.177 mmol) and 3.0 mL of 48% HBr was added to the flask. The flask was heated with a heat gun for 10 mins. The flask was cooled immediately. Deposits were seen in the reaction flask, which was extracted with diethyl ether (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield **4b,** 22.3mg, (93%); white semisolid; ^1H NMR (200 MHz, $CDCl_3$): δ 3.61 (s, 3H), 7.18-7.39 (m, 5H); ^{13}C NMR (50 MHz): δ 41.4, 127.0, 128.5, 129.5, 133.0, 177.9. CAS registry number [103-82-2].

4-chlorophenylacetic acid (4c):



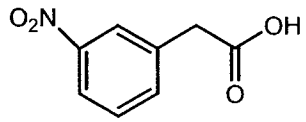
Into a flame dried flask was weighed phosphonoenamine **3c** (50 mg, 0.158mmol) and 3.0 mL of 48% HBr was added to the flask. The flask was heated with a heat gun for 10 mins. The flask was cooled immediately. Deposits were seen in the reaction flask, which was extracted with diethyl ether (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield **4c,** 25.5mg, (95%); white solid; mp 102-104 °C; ^1H NMR (200 MHz, $CDCl_3$): 3.61 (s, 3H), 7.24-7.30 (m, 4H); ^{13}C NMR (50 MHz): δ 40.4, 128.9, 130.8, 131.7, 133.5, 177.3. CAS registry number [1878-66-6].

4-nitrophenylacetic acid (4d):



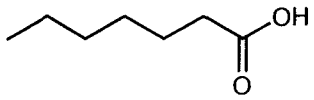
Into a flame dried flask was weighed phosphonoenamine **3e** (50 mg, 0.152 mmol) and 3.0 mL of 48% HBr was added to the flask. The flask was heated with a heat gun for 10 mins. The flask was cooled immediately. Deposits were seen in the reaction flask, which was extracted with diethyl ether (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield **4d,** 26.3mg, (98%); yellowish solid; mp 150-152 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.79 (s, 2H), 7.47 (d, J_{HH} = 8.0 Hz, 2H), 8.20 (d, J_{HH} = 8.0 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 40.7, 123.9, 130.5, 140.4, 147.4, 176.1. CAS registry number [104-03-0]. CAS registry number [104-03-0].

3-nitrophenylacetic acid (4e):



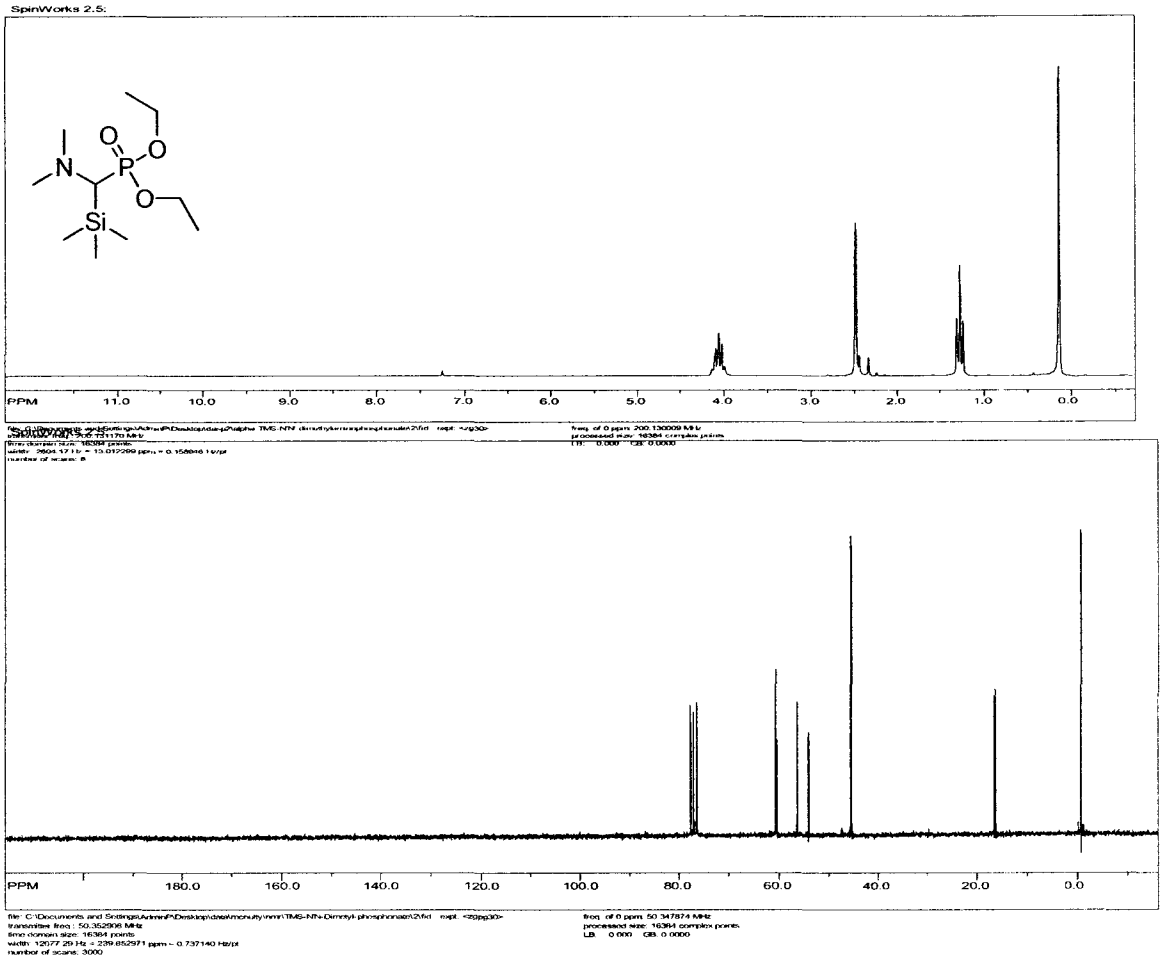
Into a flame dried flask was weighed phosphonoenamine **3f** (50 mg, 0.1524 mmol) and 3.0 mL of 48% HBr was added to the flask. The flask was heated with a heat gun for 10 mins. The flask was cooled immediately. Deposits were seen in the reaction flask, which was extracted with diethyl ether (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield **4e,** 26.2mg, (97%); yellowish solid; mp 117-119 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.51 (s, 2H), 7.43 (m, 2H), 7.98 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 47.1, 119.7, 125.1, 130.3, 135.6, 140.0, 148.6, 176.9. CAS registry number [1877-73-2].

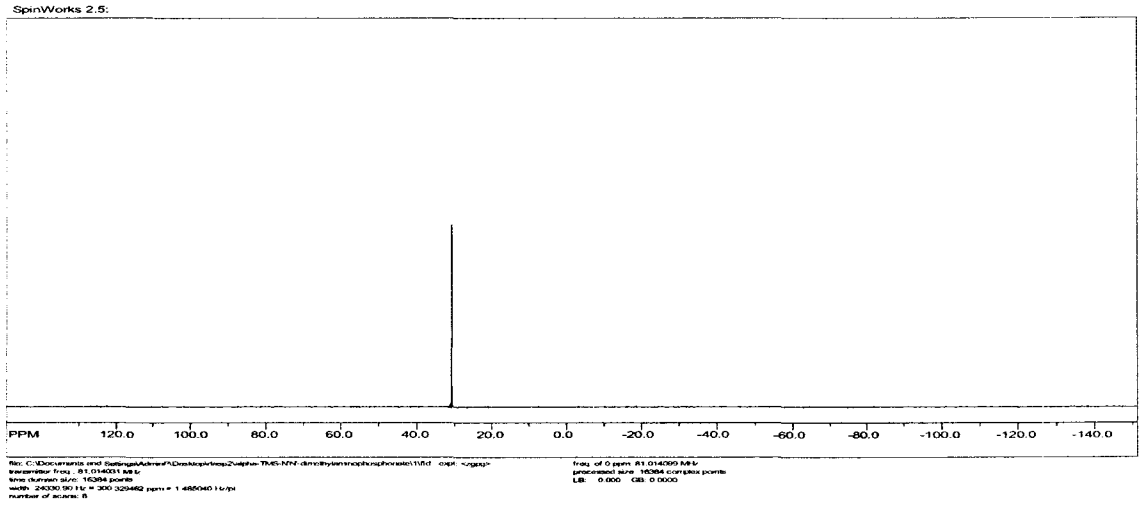
heptanoic acid (4f):

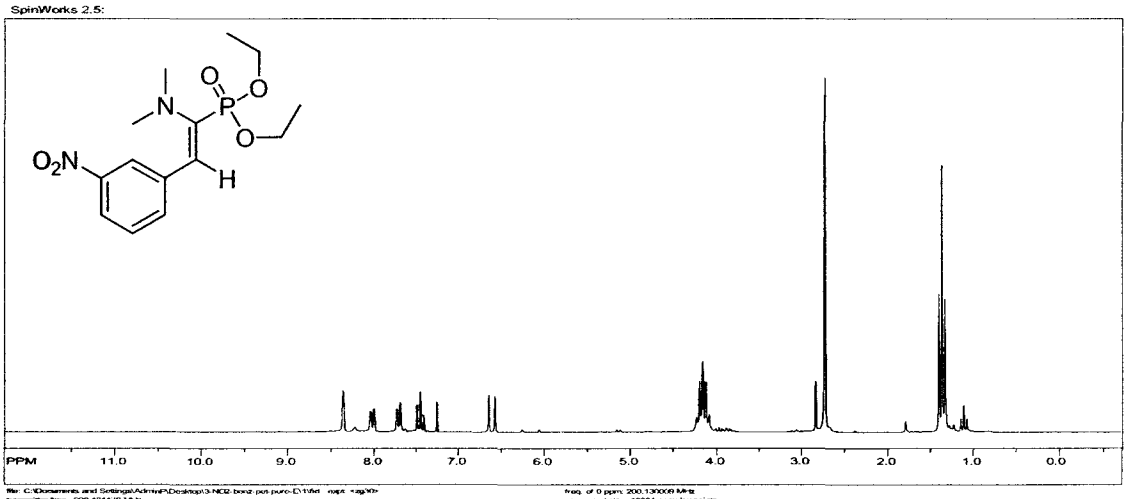


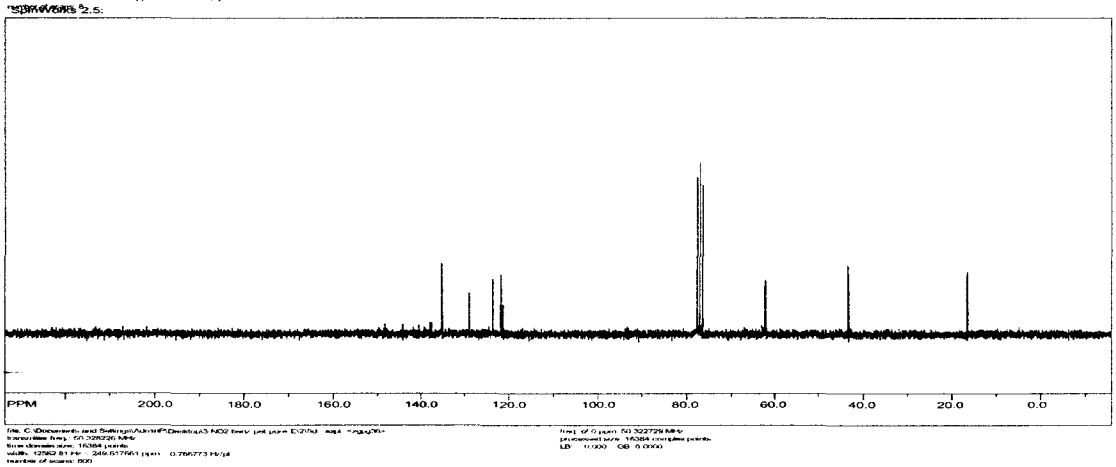
Into a flame dried flask was weighed phosphonoenamine **3g** (50 mg, 0.180 mmol) and 3.0 mL of 48% HBr was added to the flask. The flask was heated with a heat gun for 10 mins. The flask was cooled immediately. Deposits were seen in the reaction flask, which was extracted with diethyl ether (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield **4f,** 22.8mg, (97%); colorless liquid; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.89 (m, 3H), 1.20-1.40 (m, 6H), 1.63 (m, 2H), 2.34 (t, J_{HH} = 7.4 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.0, 22.7, 24.7, 28.7, 31.4, 34.3, 180.5. CAS registry number [111-14-8].

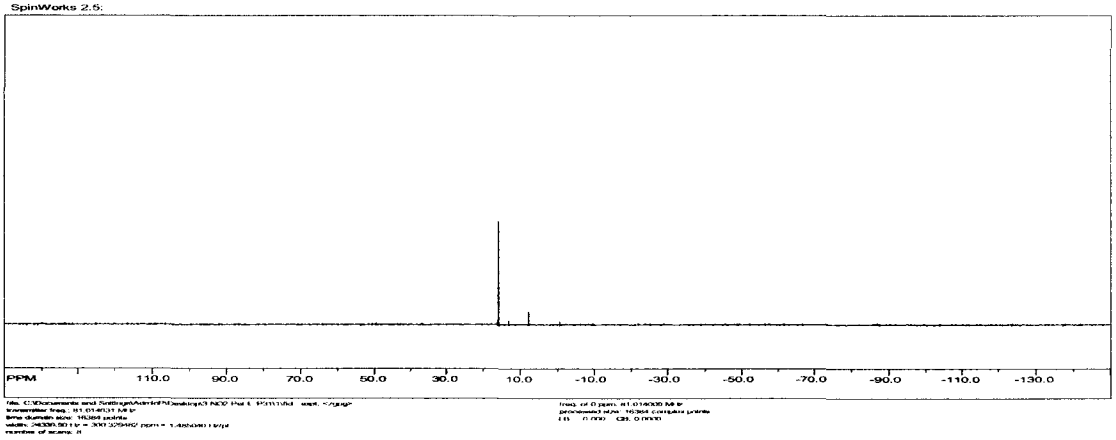
NMR Spectra of New Compounds:



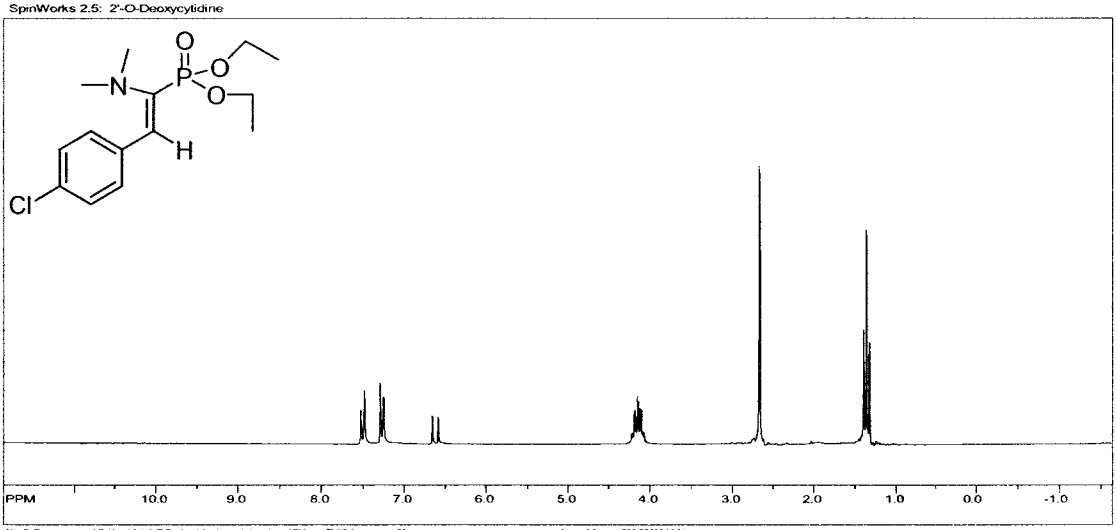



SpinWorks 2.5:
O
P
O
O
N
O_2N
H
PPM
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

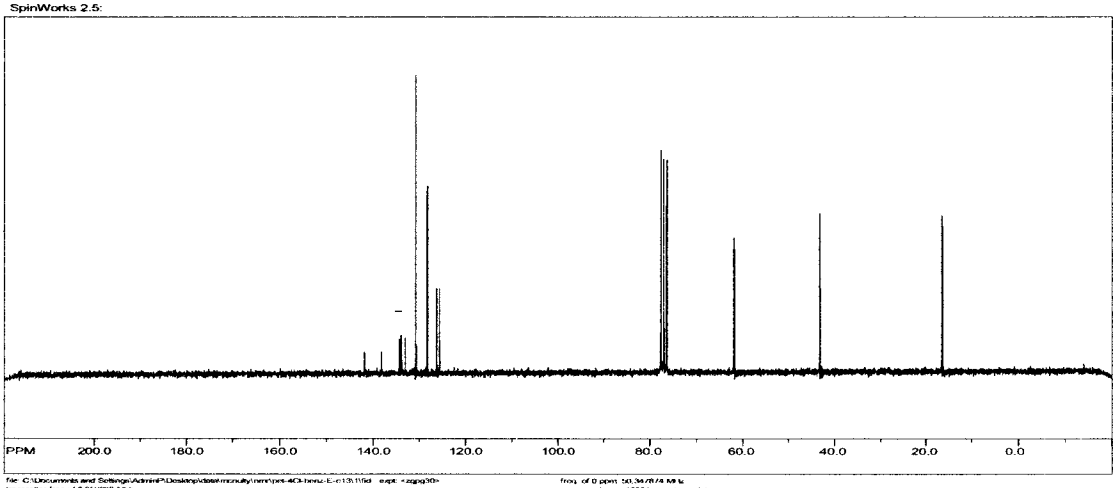

SpinWorks 2.5:
PPM
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0


SpinWorks 2.5:
PPM
110.0
90.0
70.0
50.0
30.0
10.0
-10.0
-30.0
-50.0
-70.0
-90.0
-110.0
-130.0

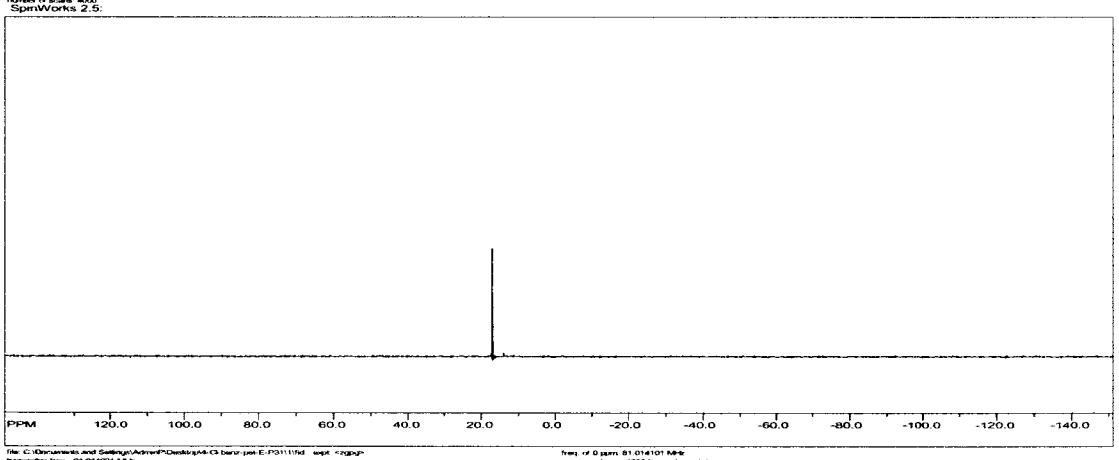
SpinWorks 2.5: 2'-O-Deoxycytidine

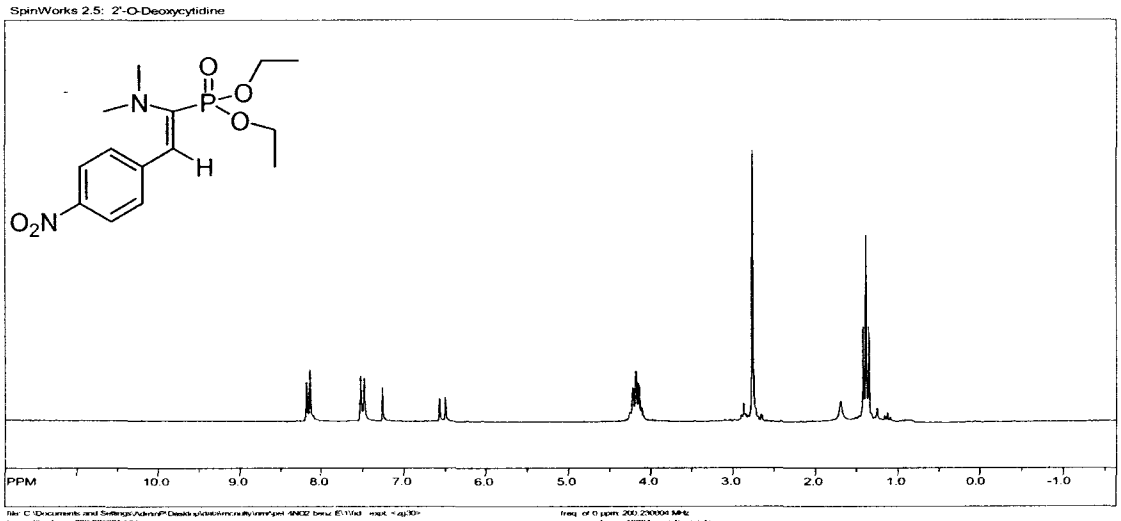


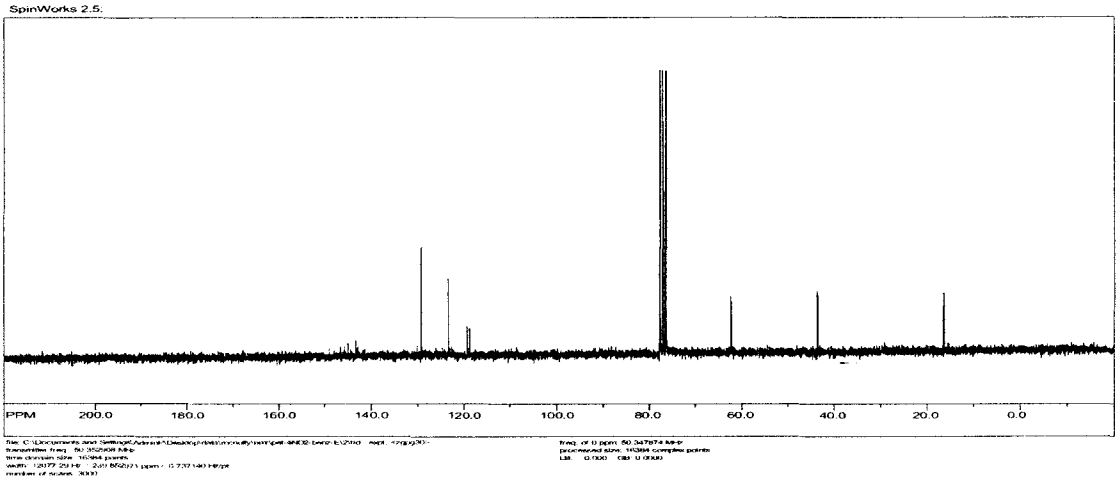
SpinWorks 2.5:

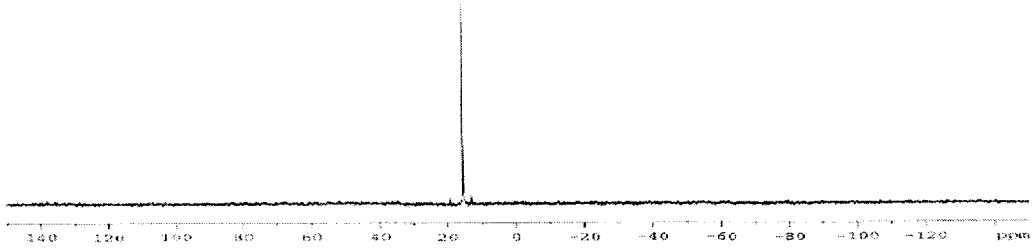


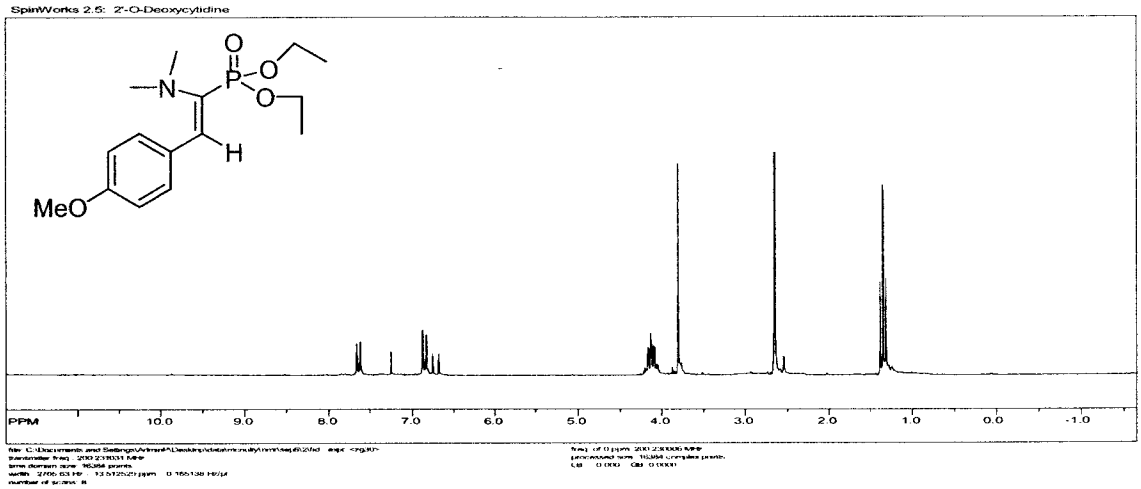
SpinWorks 2.5:

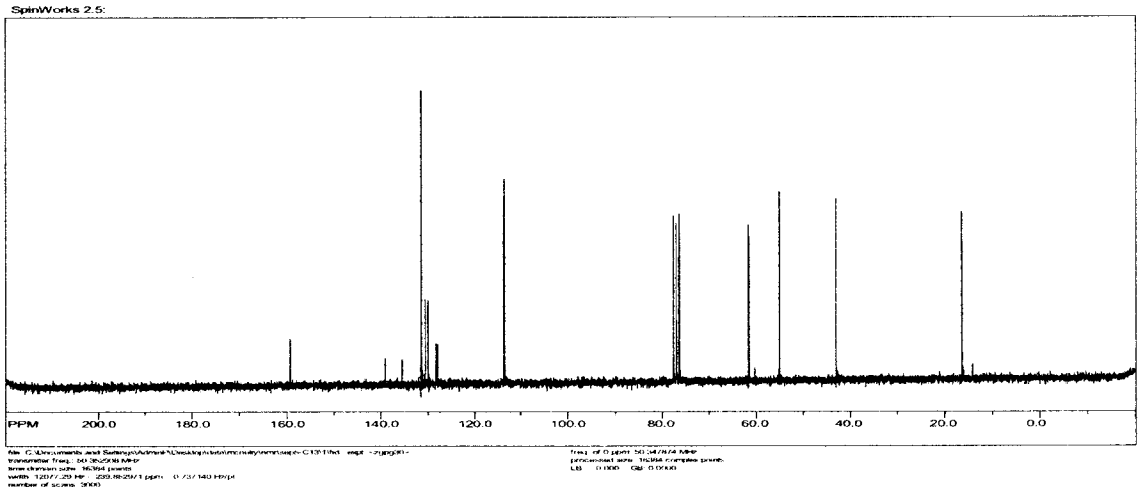


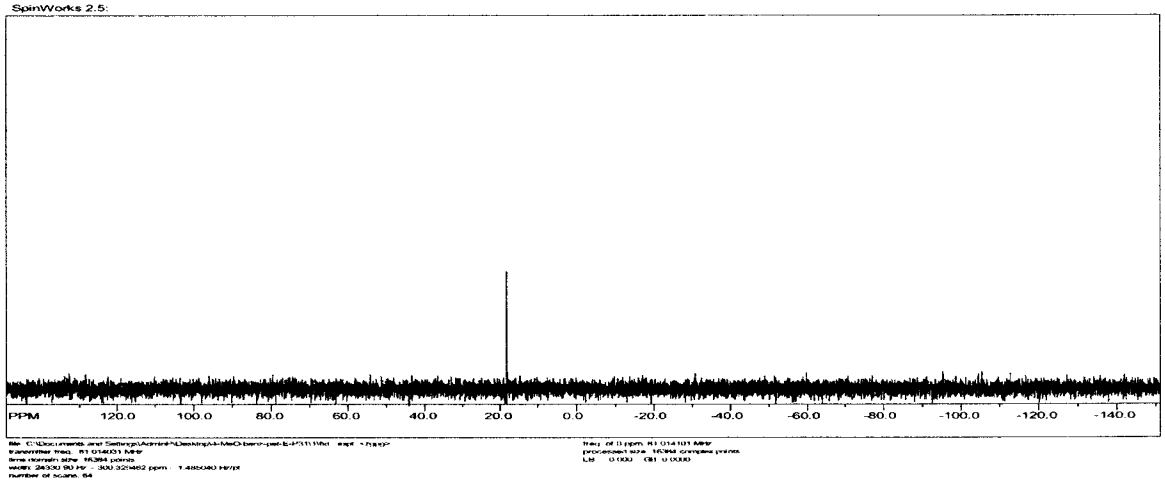

SpinWorks 2.5: 2'-O-Deoxycytidine
O
N
P
O
O
H
O2N
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0

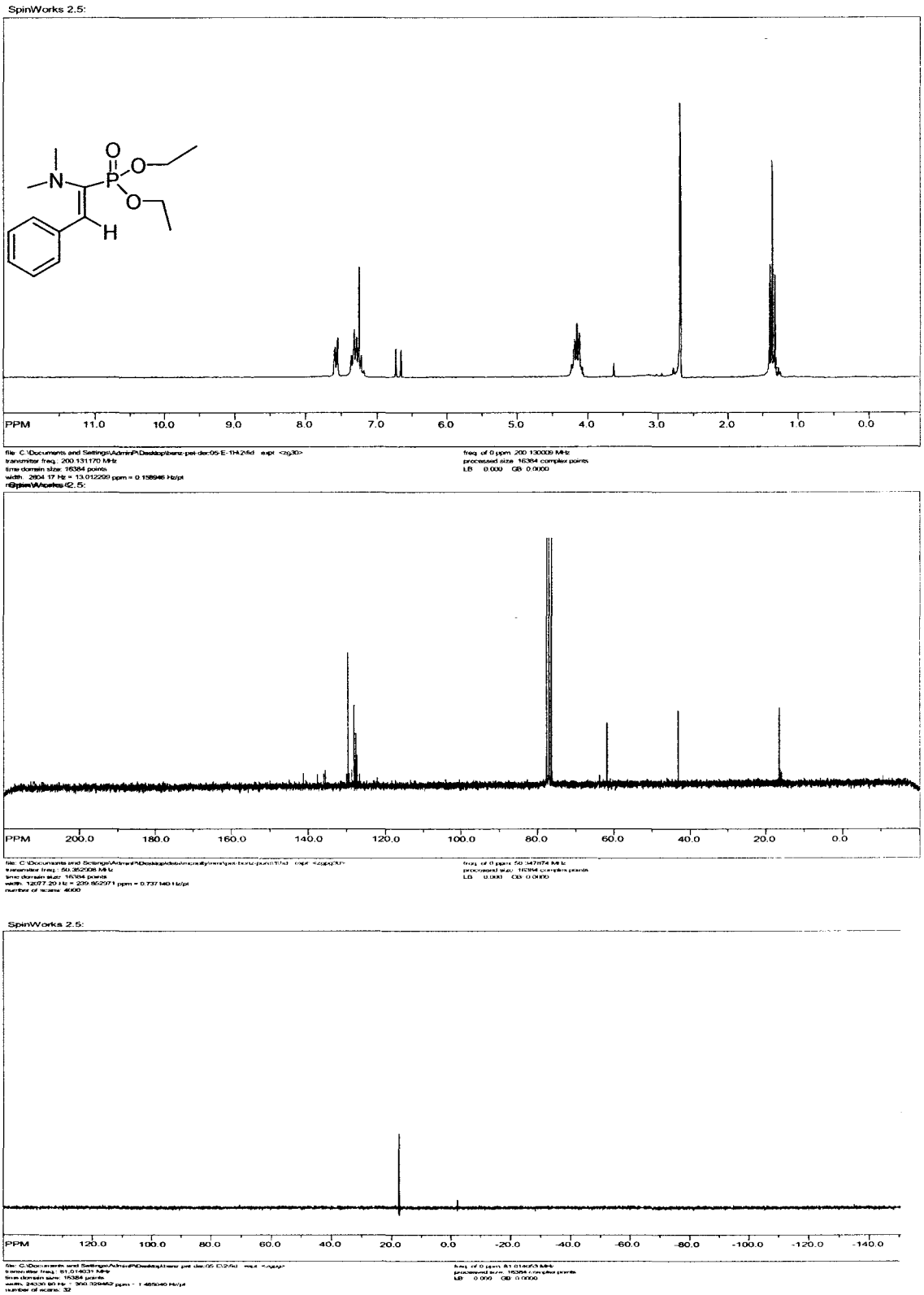

SpinWorks 2.5:
PPM
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0

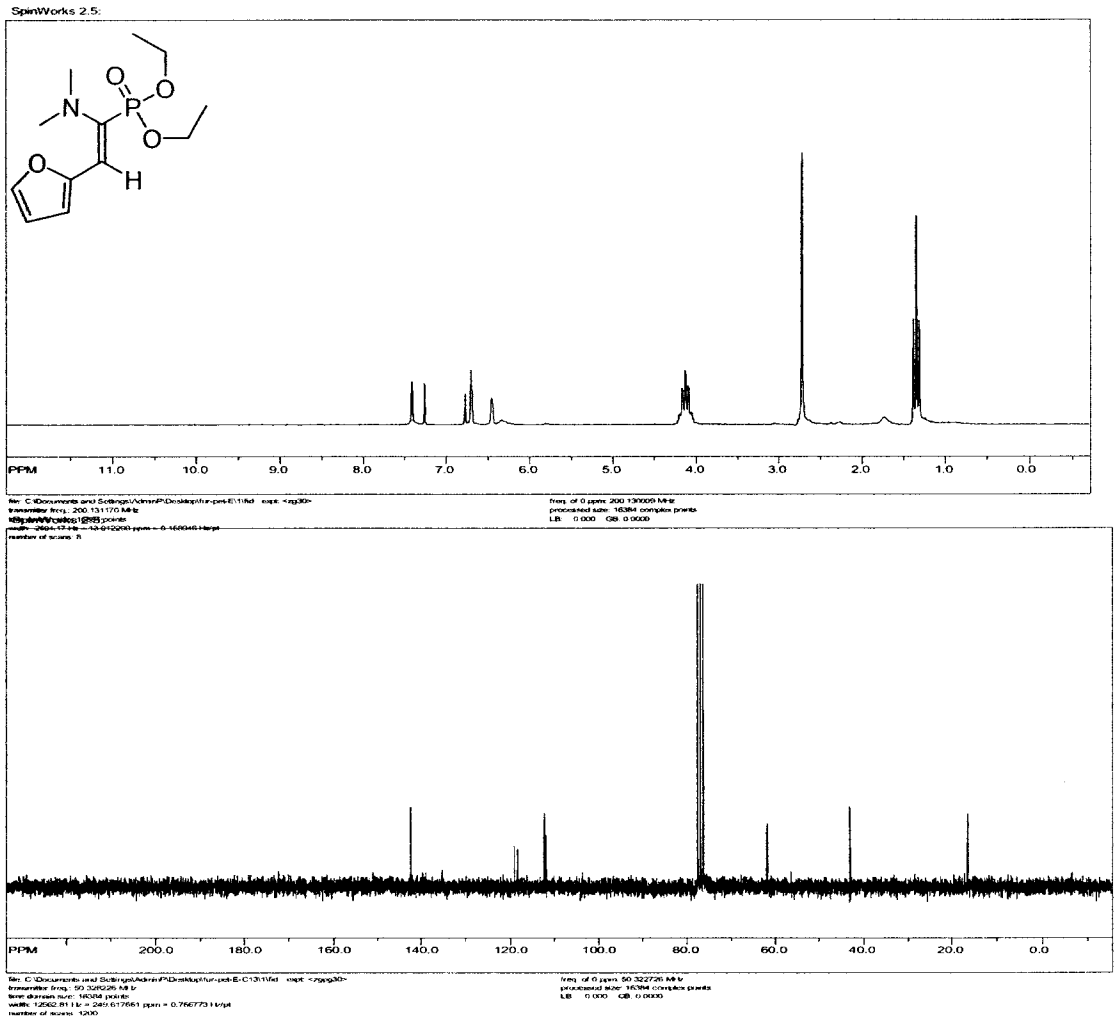

140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
ppm

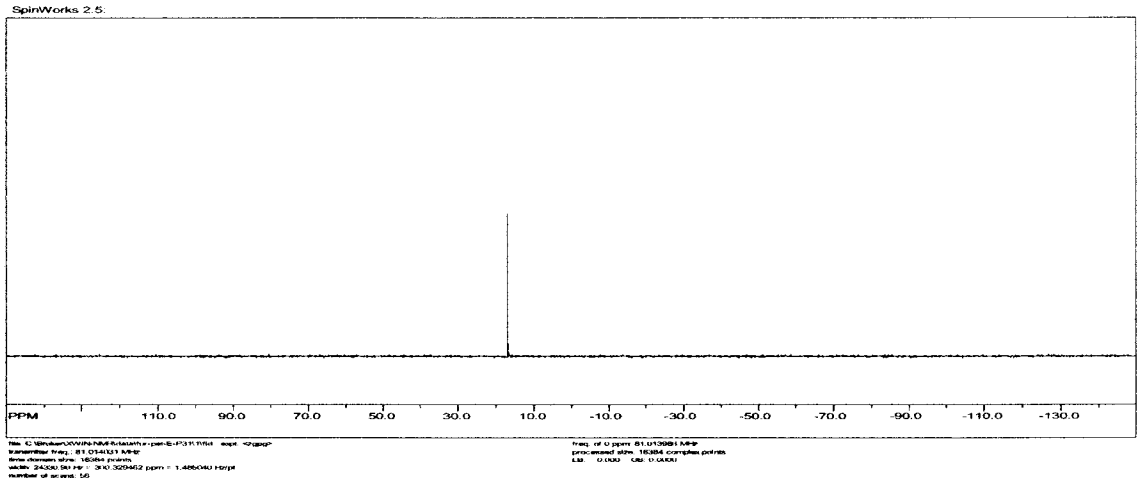

SpinWorks 2.5: 2'-O-Deoxycytidine
O
P
O
O
N
H
MeO
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0

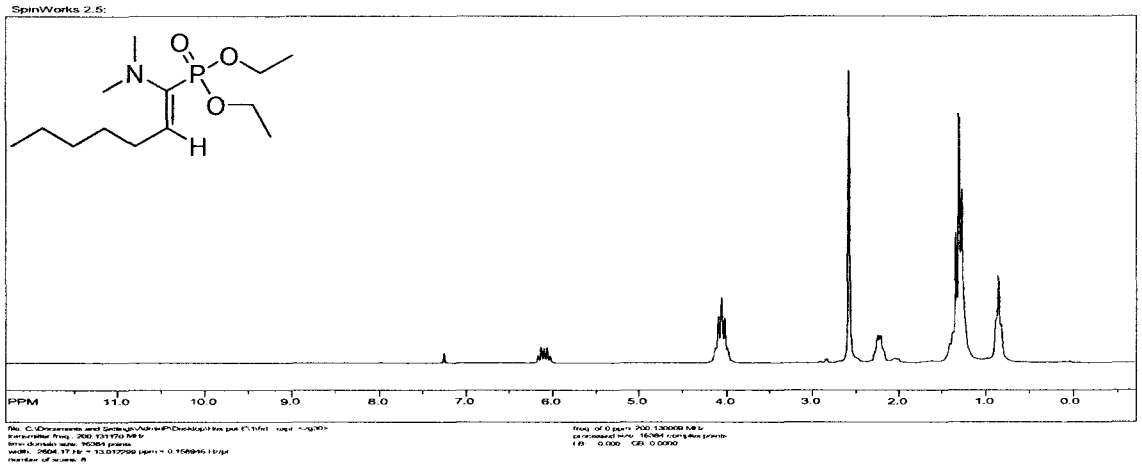

SpinWorks 2.5:
PPM
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0

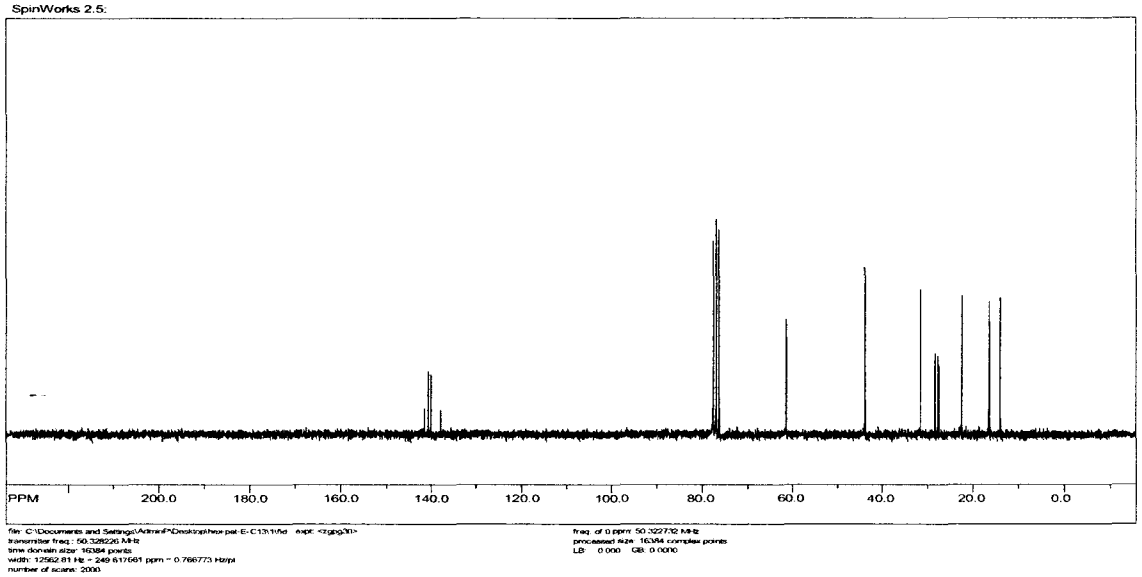

SpinWorks 2.5:
PPM
120.0
100.0
80.0
60.0
40.0
20.0
0.0
-20.0
-40.0
-60.0
-80.0
-100.0
-120.0
-140.0

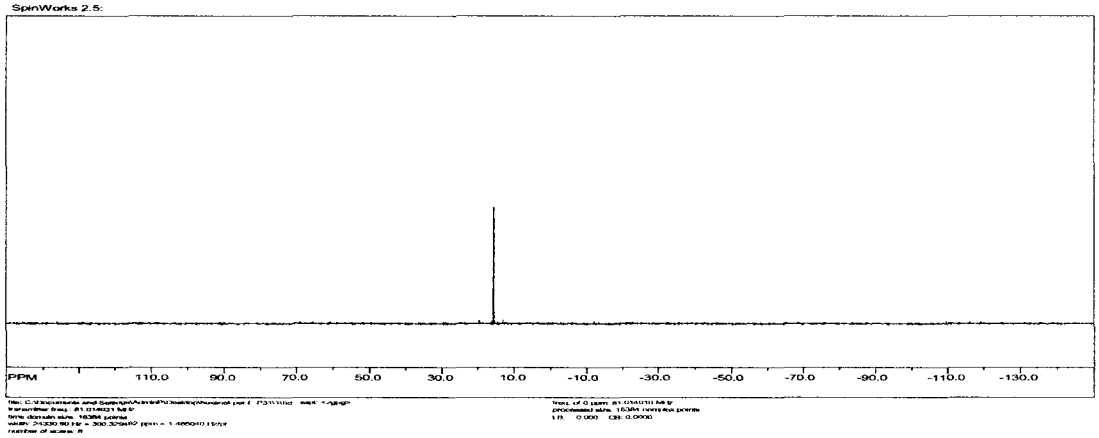

SpinWorks 2.5:
O
N
P
O
O
H
PPM
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
SpinWorks 2.5:
PPM
120.0
100.0
80.0
60.0
40.0
20.0
0.0
-20.0
-40.0
-60.0
-80.0
-100.0
-120.0
-140.0

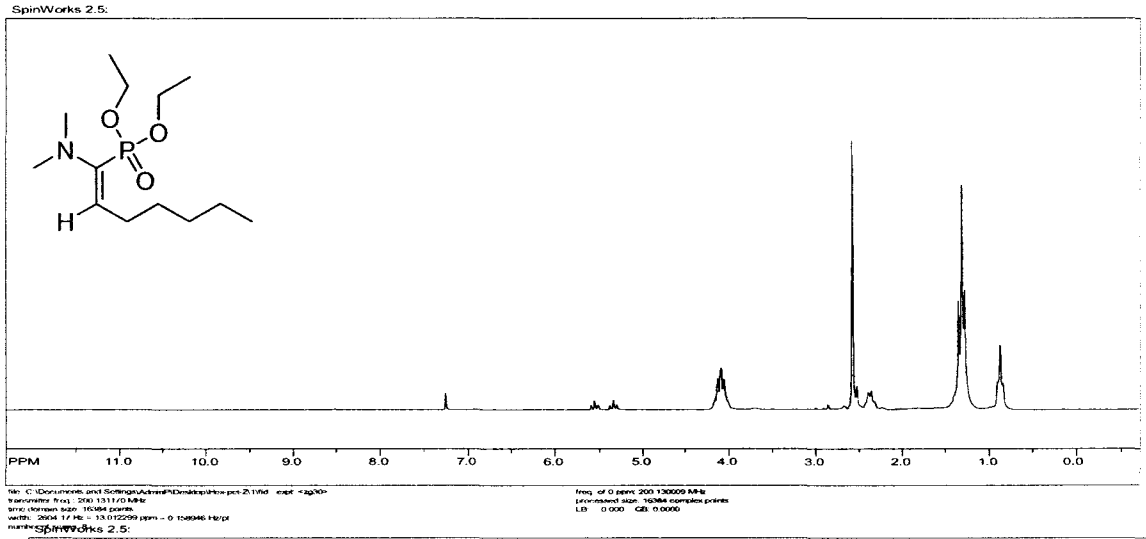

SpinWorks 2.5:
O
O
N
P
O
O
H
PPM
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0

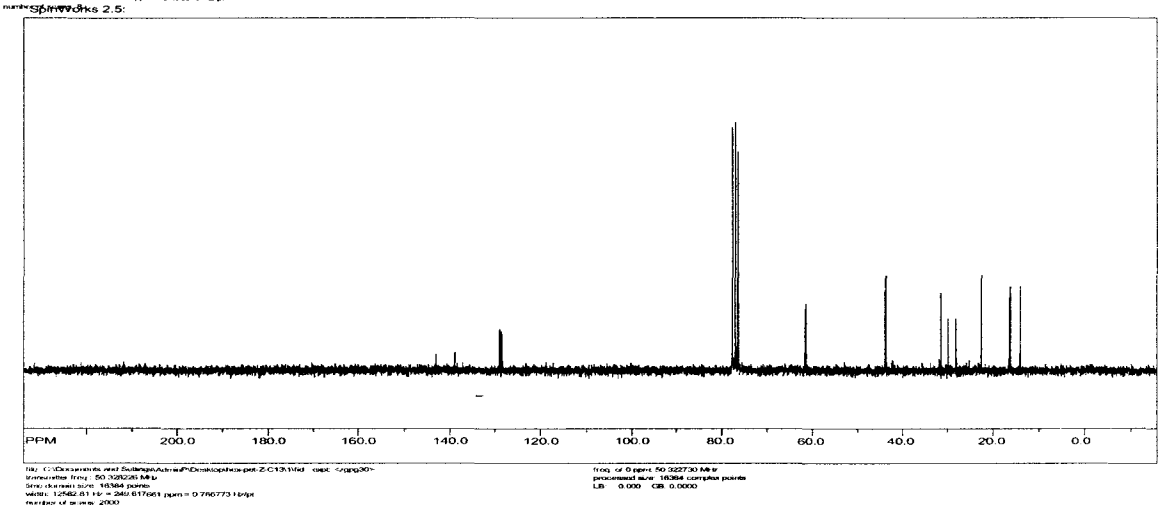

SpinWorks 2.5:
PPM
110.0
90.0
70.0
50.0
30.0
10.0
-10.0
-30.0
-50.0
-70.0
-90.0
-110.0
-130.0

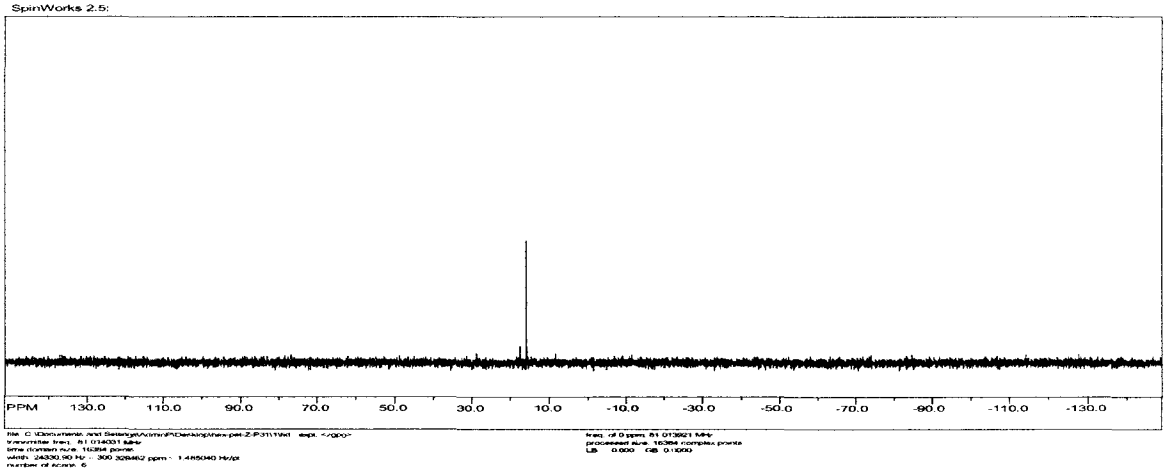

SpinWorks 2.5:
O
P
O
N
O
H
PPM
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


SpinWorks 2.5:
PPM
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0

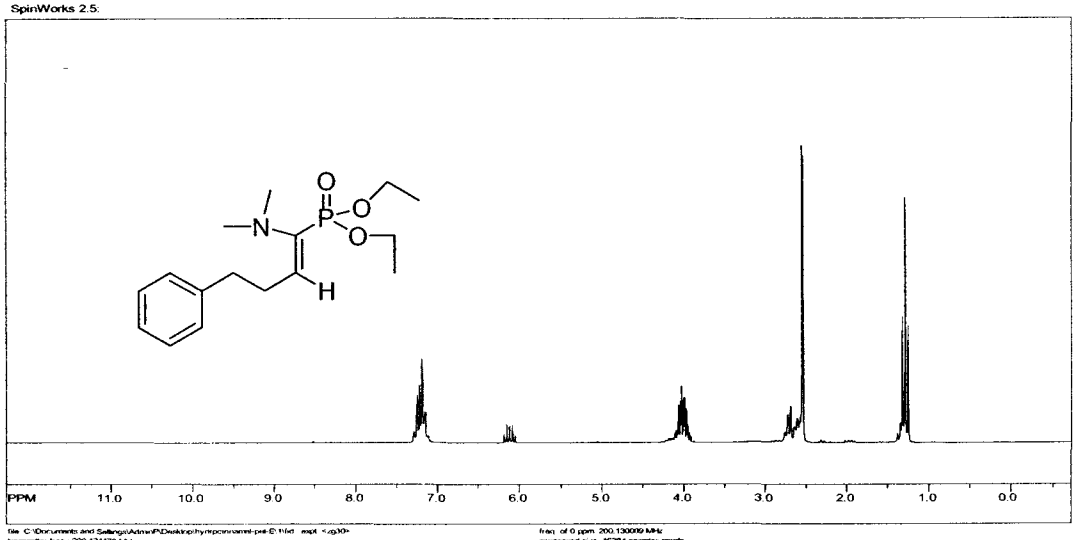

SpinWorks 2.5:
PPM
110.0
90.0
70.0
50.0
30.0
10.0
-10.0
-30.0
-50.0
-70.0
-90.0
-110.0
-130.0


SpinWorks 2.5:
O
O
N
P
O
H
PPM
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

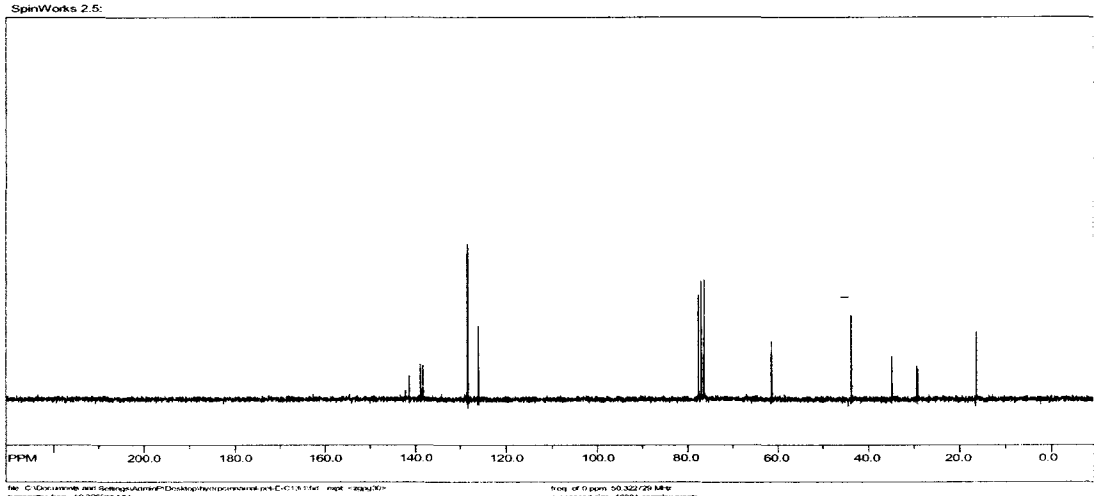

SpinWorks 2.5:
PPM
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0


SpinWorks 2.5:
PPM
130.0
110.0
90.0
70.0
50.0
30.0
10.0
-10.0
-30.0
-50.0
-70.0
-90.0
-110.0
-130.0

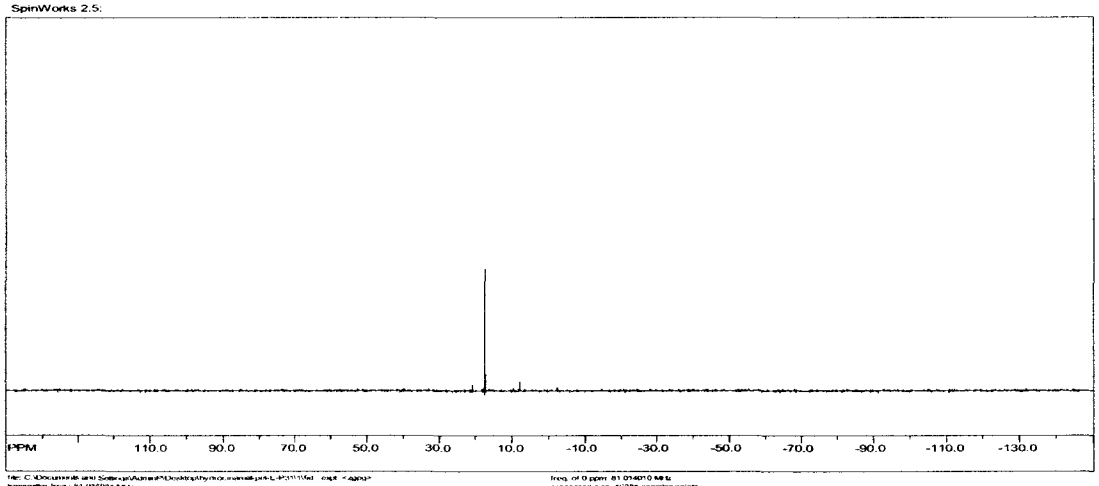
SpinWorks 2.5:

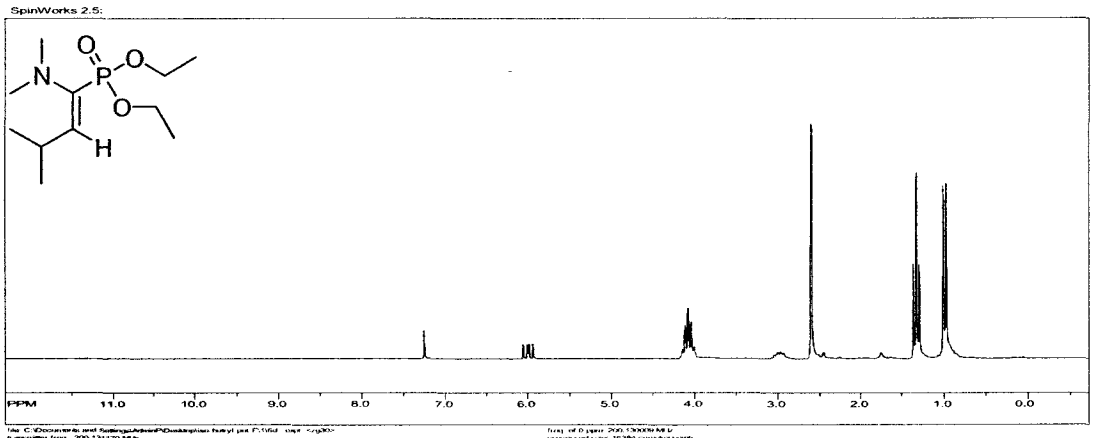


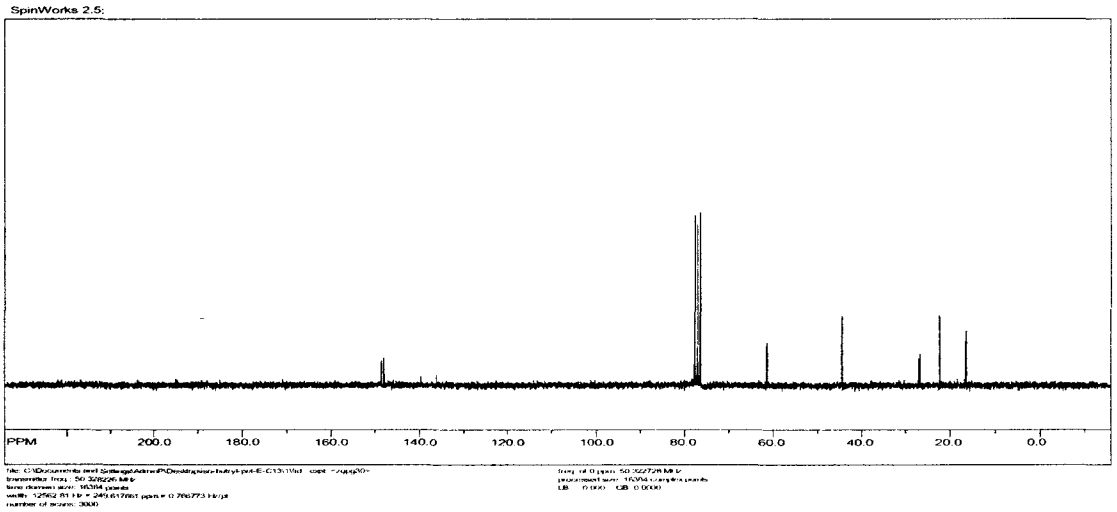
SpinWorks 2.5:

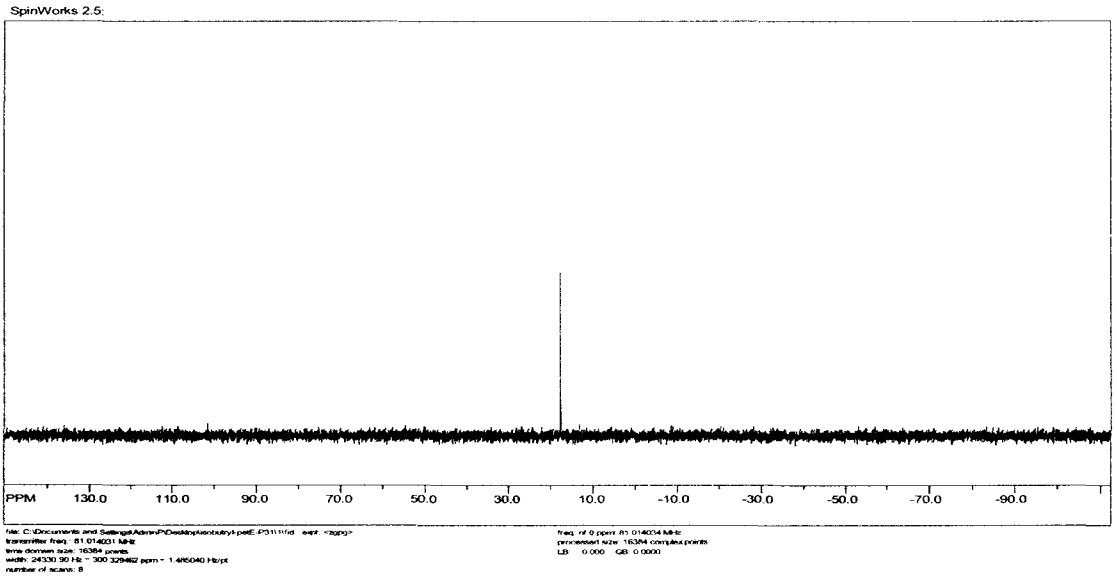


SpinWorks 2.5:

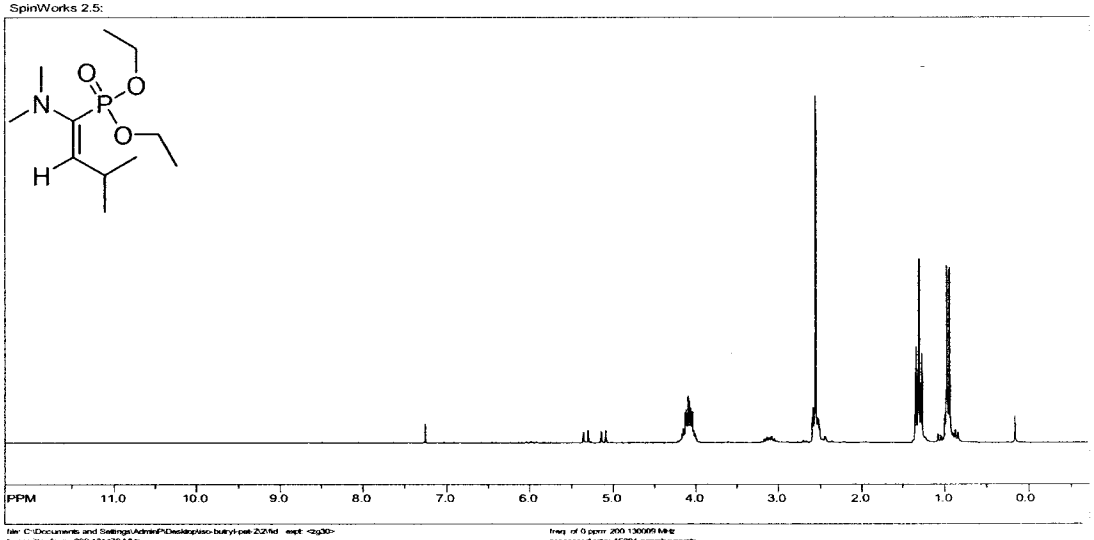



SpinWorks 2.5:
O
P
O
O
N
H
PPM
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

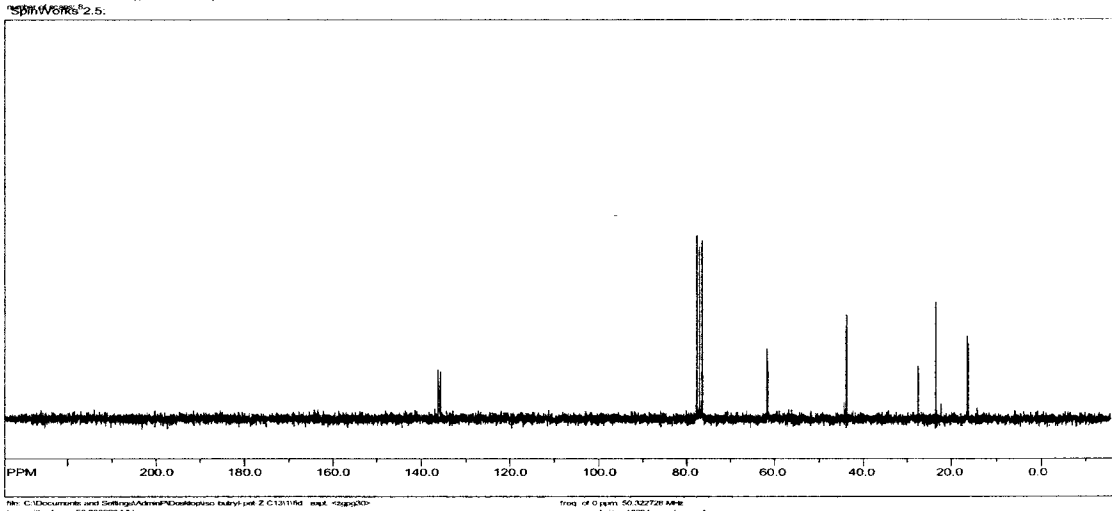

SpinWorks 2.5:
PPM
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0


SpinWorks 2.5:
PPM
130.0
110.0
90.0
70.0
50.0
30.0
10.0
-10.0
-30.0
-50.0
-70.0
-90.0

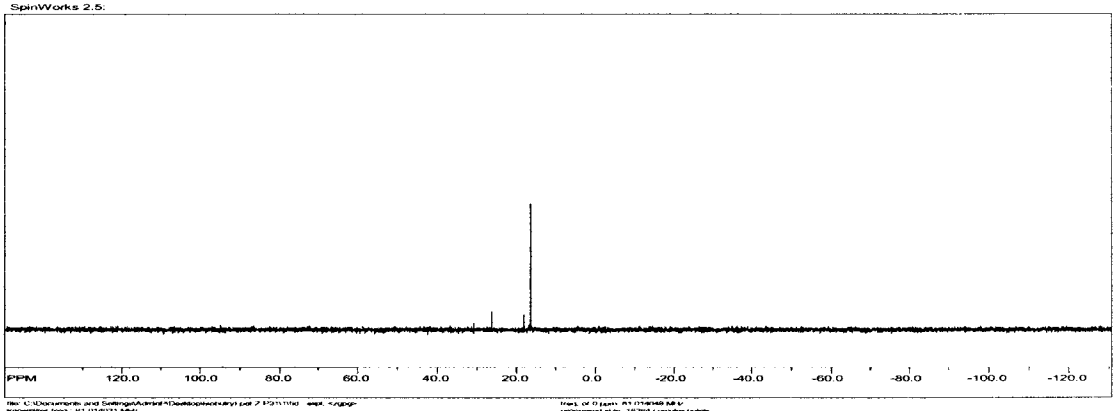
SpinWorks 2.5:

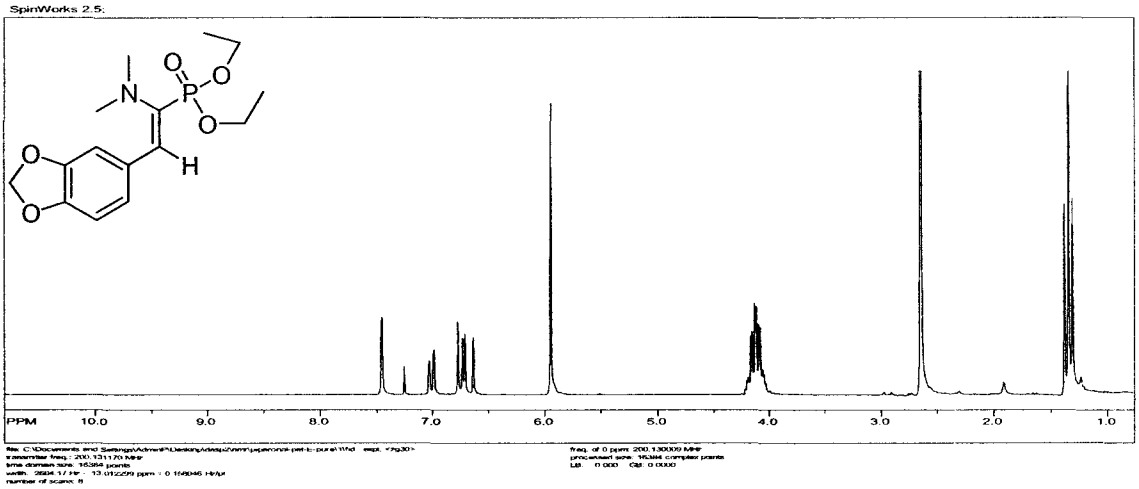


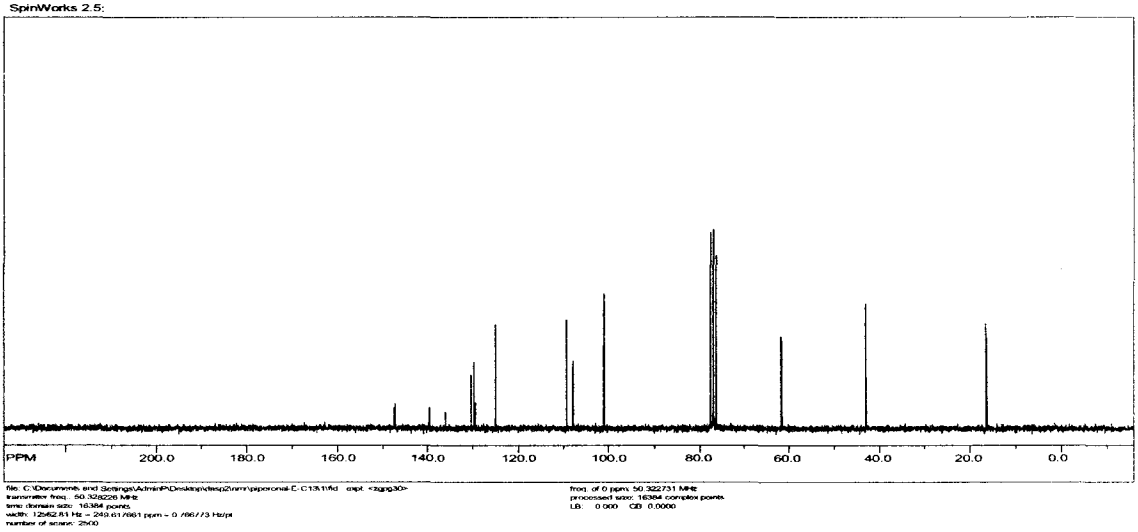
SpinWorks 2.5:

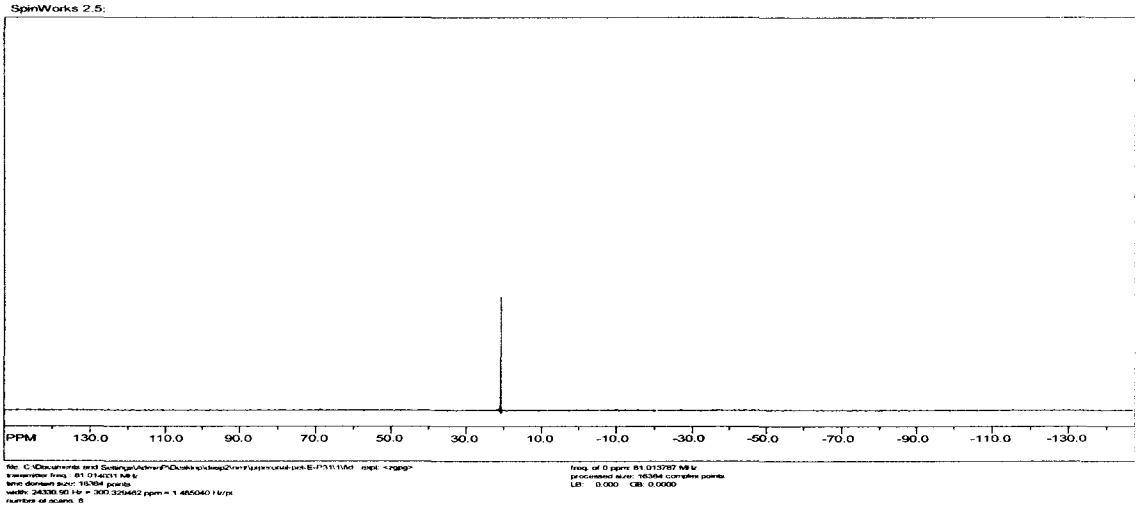


SpinWorks 2.5:




SpinWorks 2.5:
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0


SpinWorks 2.5:
PPM
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0


SpinWorks 2.5:
PPM
130.0
110.0
90.0
70.0
50.0
30.0
10.0
-10.0
-30.0
-50.0
-70.0
-90.0
-110.0
-130.0

Chapter II

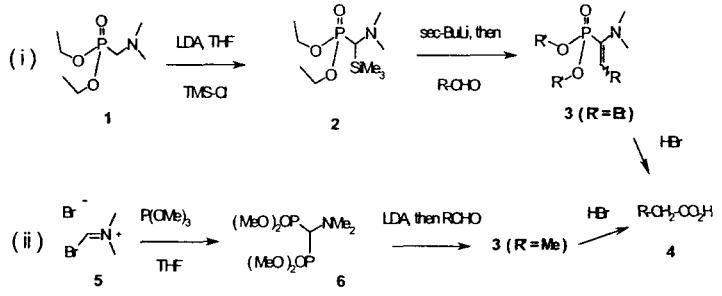
Development of a one-pot method for the homologation of aldehydes to carboxylic acids

Introduction:

The development of efficient functional group interconversions constitutes a strategic objective in synthetic organic chemistry.[1] Despite the development of many important transition-metal mediated transformations,[2] carbonyl-containing compounds continue to occupy a central role in organic synthesis by virtue of their participation in a large repertoire of predictable and controllable chemistries. Carbonyl homologation strategies have also proved to be highly useful in the conversion of the products of such reactions (aldol adducts, alkylation or Michael addition products) to an expansive array of useful intermediates. The conversion of a carbonyl compound into the corresponding one-carbon extended carboxylic acid is potentially of great value due to the wide occurrence and versatility of these functional groups in organic synthesis.[3]

Not surprisingly, several methods have been developed to achieve this transformation, usually requiring two or three steps.[4] The most efficient method to date is the benzotriazole method of Katritzky et al employing a Peterson reaction that allowed for the one-pot interconversion of a range of aldehydes to homologated carboxylic acids in 45 to 57% yield.[4f] Most other methods are multistep, employ reagents that are not readily available or suffer from harsh conditions,[4] resulting in poor to moderate overal yields (typically 35-60%). As a result, there is still a need to develop an operationally simple and efficient synthetic procedure using readily available reagents for this desrirable transformation, ideally in a single step.

Gross and Costisella[4b] and Degenhardt[6a] reported the use of α–phosphonoenamines as a route for this homologation reaction using the anion derived from the *bis*-diethylphosphonate ester of **6**, Scheme 1. We recently reported[4n] an improved method employing a Peterson reaction of the α–trimethylsilyl derivative **2** in accord with previous studies by Dufrechou[6b] (Scheme 1, line i). The major obstacle toward application of this biphosphonate route to carbonyl homologation is the lack of an efficient method for the generation of phosphonoenamines **3** from aldehydes. While the electronic effect exerted in the silicon-directed route allows a more efficient (70 to 87% yield[4n] versus 8 to 69%[6b]) access to the phosphonoenamine intermediates, our previous results indicated that steric factors might be detrimental to the aldehyde addition step. As an extension of this method, we generated the less sterically demanding 1,1-bis-dimethylphosphonate intermediate of structural type **6** (Scheme 1, line ii). Herein we report that the lithium carbanion derived from **6** reacts with aldehydes to give the desired α-phosphonoenamines in high yield. We also report a further imrpoved method for the acid promoted hydrolysis. This new protocol provides for the most efficient route to date for the aldehyde to homolgated carboxylic acid synthetic interconversion, which can be effectively conducted in a one-pot process.



Scheme1: Aldehyde to carboxylic acid homologation strategies via phosphonoenamine intermediates 3

Results & Discussion:

The reaction of the commercially available (bromomethylene)- dimethyliminium bromide[5] **5** with two equivalents of trimethylphosphite yielded the isolatable 1,1-bisphosphonate **6** (Scheme 1). Sequential treatment of **6** with 1.1 equivalents of LDA in THF at -78 °C followed by addition of 1 equivalent of 4-nitrobenzaldehyde yielded the isolatable phosphonoenamine derivative **3** (Scheme 1, R'=Me, R=4-(NO_2)C_6H_4-). Interestingly, we note that α-phosphonoenamine intermediates have themselves been shown to possess biological activities.[7] In this case; the phosphonoenamine could be isolated in 92-93% yield. Acidic hydrolysis of **3** employing 48 % HBr and brief microwave irradiation (100 °C for 3 min.) yielded the homologated 4-nitrophenylacetic acid in >98% isolated yield.

We next developed a protocol that allows all of the chemistry described to be conducted efficiently in one flask. A vacuum strip of solvent was introduced after formation of the bisphosphonate **6** to remove traces of bromomethane due to its potential reactivity with the enamine. Sequential addition of base followed by aldehyde led to the formation of **3**. While the direct introduction of aqueous HBr after the Horner reaction (conversion of **3** to **4**) and conventional heating (100 °C, 10 min.) completed the hydrolysis effectively,[4n] we have also now found that microwave irradiation (100 °C, 3 min.) effects rapid hydrolysis. The homologated acids are isolated efficiently without the need for chromatographic purification employing a simple base extraction, separation and re-acidification work-up protocol.

The scope of this one-pot interconversion was investigated with a range of aromatic and aliphatic aldehydes, the results of which are presented in Table 1. No major electronic

effect was observed as electron rich and electron deficient aldehydes all yielded the corresponding phenylacetic acid derivatives in high isolated yield, although yields appear to be slightly higher with more reactive aldehydes.

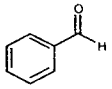
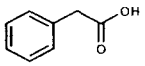
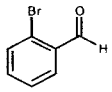
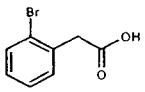
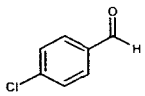
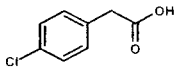
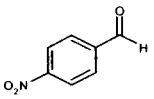
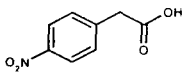
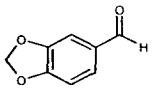
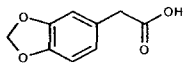
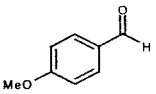
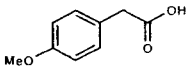
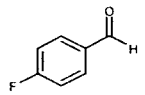
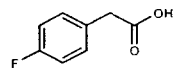
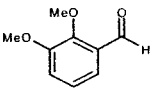
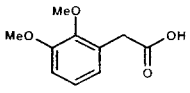
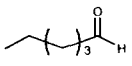
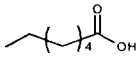
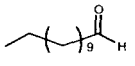
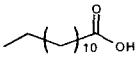
Entry	RCHO	RCH_2CO_2H	Yield (%)
1			83
2			90
3			80
4			88
5			82
6			80
7			85
8			79
9			75
10			77

Table 1 One-carbon homologation of aldehydes to carboxylic acids

In addition, hindered *ortho*-substituted aldehydes could be employed (entries 2 and 8) effectively. We also demonstrated that enolizable aliphatic aldehydes (entries 9 and 10) yielded the homologated acids in good isolated yield following the same reaction and work-up protocol.

The overall results are consistent with lower aldol-type reactivity of non-activated aromatic aldehydes, hindered aldehydes and enolizable aldehydes, and are evidence that the carbonyl addition step is still sluggish. Nonetheless, the sterically less demanding *bis*-dimethylphosphonate allows for a very efficient general synthesis of α-phosphonoenamines in comparison to its ethyl ester analog,[6a] and shows that high yields of phosphonoenamines can be attained without recourse to α–silylation.[4n,6]

Conclusion:

In conclusion, we have demonstrated that the commercially available salt (bromomethylene)-dimethyliminium bromide **5** reacts with trimethylphosphite providing the 1,1-bisphosphonate derivative **6** and that the anion derived from **6** reacts with aldehydes yielding phosphonoenamines **3,** the controlled hydrolysis of which provides homologated carboxylic acid derivatives in high yield. A general, one-pot procedure was developed successfully employing both aromatic and aliphatic aldehydes allowing for the achievement of this desirable interconversion in high yield for the first time. Further developments of the methodology and synthetic applications are currently under investigation in our laboratories.

References:

1. Over 20 marketed pharmaceuticals are phenylacetate derivatives including diclofenac (anti-arthritic), ibufenac (anti-inflammatory), ritalin (anti-ADHD), homovanillic acid (schizophrenia), propanidid (anesthetic), guanfacine (antihypertensive) and 4-chlorophenylacetic acid (anti-neoplastic). For a selection of examples see: (a) Failli, A. A.; Kreft, A. F.; Musser, J. H . U.S. Patent, **1991**, 5,021,576. (b) Nahar, L.; Russel, W.R; Middleton, M.; Shoeb, M.; Sarker, S. D. *Acta. Pharm.* **2005**, 55, 187-

193. (c) Santini, C.; Berger, G. D.;. Han, W.; Mosley, R.; MacNaul, K.; Berger, J.; Doebber, T.; Wu, M.; Moller, D.E.; Tolman, R.L.; Sahoo, S. P. *Bioorg. & Med. Chem. Lett.* **2003**, 13, 1277-1280. (d) Rakowitz, D. ; Gmeiner, A.; Schroder, N.; Matuszczak, B. *Eur. J. Pharm. Sci.* **2006**, 27, 188-193. (e) Sidell, N.; Kirma, N.; Morgan, E. T.; Nair, H.; Tekmal, R. R. *Cancer Lett.* **2007**, 251, 302-310.

2. For a selection of synthetic applications see: (a) Gore, M.P.; Vederas, J.C. *J. Org. Chem.* **1986**, 51, 3700-3704. (b) Prashad, M.; Kim, H.Y.; Har, D.; Repic, O.; Blacklock, T.J. *Tetrahedron Lett.* **1998**, 39, 9369-9372. (c) Wittenberger, S.J.; McLaughlin, M.A. *Tetrahedron Lett.* **1999**, 40, 7175-7178. (d) Bull, S.D.; Davies, S.G.; Key, M.S.; Nicholson, R.L.; Savory, E.D. *Chem. Commun.* **2000**, 1721-1722. (e) McNulty, J.; Nair, J. J.; Sliwinski, M.; Harrington, L.E.; Pandey, S. *Eur. J. Org. Chem.* **2007**, 5669-5673. (f) McNulty, J.; Nair, J. J.; Pandey, S.; Griffin, C. *J. Nat. Prod.* **2008**, 71, 357-363.

3. (a) Kohlpaintner, C. W.; Beller, M. *J. Mol. Cat. A: Chem.* **1997**, 116, 259-267. (b) Adams, R.; Thal, A. F. *Org. Synth.* **1922**, 2, 9-11. (c) Adams, R.; Thal, A. F. *Org. Synth.* **1922**, 2, 27-28.

4. (a) Corey, E. J.; Markl, G. *Tetrahedron Lett.* **1967**, 33, 3201-3204. (b) Gross, H.; Costisella, B. *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 391-392. (c) Schollkopf, U.; Schroder, R. *Angew. Chem. Int. Ed. Engl.* **1972**, 11, 311-312. (d) Jones, P. F., Lappert, M. F. *J. Chem. Soc., Chem., Commun.* **1972**, 526. (e) White, D. R.; Wu, D. K. *J. Chem. Soc., Chem., Commun.* **1974**, 988-989. (f) Dinizo, S. E.; Freerksen, R. W. ; Papst, W. E.; Watt, D. S. *J. Am. Chem. Soc.* **1977**, 99, 182-186. (g) Gross, H.; Costisella, B. *Tetrahedron* **1982**, 38, 139-145. (h) Takahashi, K.; Shibasaki, K.;

Ogura, K; Iida, H. *J. Org. Chem.* **1983**, 48, 3566-3569. (i) Takahashi, K.; Msuda, T.; Ogura, K; Iida, H. *Synthesis* **1983**, 1043-1045. (j) Hiyama, T.; Inoue, M.; Saito, K. *Synthesis* **1986**, 645-647. (k) Katritzky, A. R.; Dorin, T.; Linghong, X. *Synthesis* **1996**, 1425-1427. (l) Satoh, T.; Nakamura, A.; Iriuchijima, A.; Hayashi, Y.; Kubota, K. *Tetrahedron* **2001**, 57, 9689-9696. (m) Huh, D. K.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, G. *Tetrahedron* **2002**, 58, 9925-9932. (n) Zhou, G. B.; Zhang P. F.; Pan, Y. J. *Tetrahedron* **2005**, 61, 5671-5677. (o) McNulty, J.; Das, P.; Gosciniak, D. *Tetrahedron Lett.* **2008**, 49, 281-285.

5. This reagent is available from the Aldrich Chemical Company.

6. (a) Degenhardt, C. R. *Synth. Commun.* **1982**, 12, 415-421. (b). Dufrechou, S; Combret, J. C.; Malhiac, C.; Collignon, N. *Phosphorus, Sulphur & Silicon* **1997**, 127, 1-14.

7. F. Zumstein and F. Klingseisen, *Ger. Offen.* **1990**, DE 4029444 A1.

Experimental:

General Information:

Reactions were carried out under argon in oven-dried glassware. Diethyl-2-N,N-dimethylaminomethano phosphonate was obtained from Cytec, all other fine chemicals were obtained from Aldrich. *s*-Butyl lithium was obtained from Aldrich as a 1.4 M solution in cyclohexane. THF was distilled from sodium with benzophenone indicator. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV and HRMS (EI) were performed with Micromass Q-Tof Ultima spectrometer. ^{1}H and ^{13}C spectra were recorded on a Bruker 200 and AV 600 spectrometer in $CDCl_3$ with TMS as internal standard; chemical shifts (δ) are reported in ppm downfield of TMS and coupling constants (*J*) are expressed in Hz. The (*E*) to (*Z*) ratios were determined from the relative integration of the ^{1}H NMR spectra for the olefinic protons. Microwave reactions were performed in crimp-capped vials using a Biotage Initiator 2.5 reactor. Thin layer chromatography was performed on Macherey-Nagel SIL-G/UV_{254} plates and column chromatography performed over Merck 70-230 mesh silica gel.

General one-pot procedure for the synthesis of homologated carboxylic acids:

Into a flame-dried microwave vial, containing a magnetic stirring bar, was weighed (bromomethylene)-dimethyliminium bromide (1.0 mmol) under Ar and dry THF (2 mL) was added. The flask was septa-sealed and stirred for 15 min under Ar at room temperature whereupon $P(OMe)_3$ (2.0 mmol) was added slowly. After 40 min. the solvent was removed under argon flow and the concentrate vacuum dried for 20 min giving **6.** THF (2 mL) was added and the vial cooled to -78 °C under Ar for 15 min whereupon

LDA (1.1 mmol, 2.0 M stock, heptane/THF/ethylbenzene) was added slowly. After 40 min a 0.5 M solution (in THF) of the corresponding aldehyde (1.05 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The THF was removed under Ar and 3 mL of 48% HBr was added to the residue. The vial was now crimp-capped and irradiated in the microwave at 100°C for 3 min. The resulting mixture was extracted with diethylether (3 x 15 mL). The combined organic layers were partitioned with 10 mL of (10% w/v) aqueous NaOH allowing clean phase separation (15 min). The ether was extracted with water (2x 10 mL). The combined aqueous layers were carefully acidified (10% w/v aqueous HCl) and the resulting mixture was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield the corresponding homologated carboxylic acid in pure form.

3'4-(Methylenedioxy)phenylacetic acid (4a):[1]

Mp 125-127 °C (lit.[2] 125-127 °C); yield 82%; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.57 (s, 2H), 5.91 (s, 2H), 6.71-6.81 (m, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 41.4, 107.8, 109.3, 123.2, 127.7, 146.8, 147.9, 177.6.

Phenylacetic acid (4b):[3]

Mp 75-77 °C (lit.[3] 76-78 °C); yield 83%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.61 (s, 3H), 7.18-7.39 (m, 5H); ^{13}C NMR (50 MHz): δ 41.4, 127.0, 128.5, 129.5, 133.0, 177.9.

4-Chlorophenylacetic acid (4c):[4]

Mp 104-105 °C (lit.[4] 104-106 °C); yield 80%; ^{1}H NMR (200 MHz, $CDCl_3$): 3.61 (s, 3H), 7.24-7.30 (m, 4H); ^{13}C NMR (50 MHz): δ 40.4, 128.9, 130.8, 131.7, 133.5, 177.3.

4-Nitrophenylacetic acid (4d):[5]

Mp 149-150 °C; yield 88%; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.79 (s, 2H), 7.47 (d, J_{HH} = 8.0 Hz, 2H), 8.20 (d, J_{HH} = 8.0 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 40.7, 123.9, 130.5, 140.4, 147.4, 176.1.

3-Nitrophenylacetic acid (4e):[3]

Mp 117-118 °C (lit.[3] 118-120 °C); yield 80%; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.51 (s, 2H), 7.43 (m, 2H), 7.98 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 47.1, 119.7, 125.1, 130.3, 135.6, 140.0, 148.6, 176.9.

Heptanoic acid (4f):[6]

Yield 75%; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.89 (m, 3H), 1.20-1.40 (m, 6H), 1.63 (m, 2H), 2.34 (t, J_{HH} = 7.4 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.0, 22.7, 24.7, 28.7, 31.4, 34.3, 180.5.

4-Methoxyphenylacetic acid (4g):[7]

Mp 84-86 °C (lit.[3] 85-87 °C); yield 80%; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.63 (s, 2H), 3.77 (s, 3H), 6.83 (2, J_{HH} = 7.7 Hz, 2H), 7.22 (d, J_{HH} = 7.7 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 40.1, 56.2, 114.5, 125.6, 130.4, 159.0, 178.2.

4-Fluorophenylacetic acid (4h):[8]

Mp 83-84 °C (lit.[3] 82-85 °C); yield 85%; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.61 (s, 2H), 7.03-7.23 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 40.1, 115.6, 128.7, 130.9, 160.9, 177.5.

2'3-Dimethoxyphenylacetic acid (4i):[9]

Mp 82-83 °C (lit.[9] 84 °C); yield 79%; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 2H), 3.87 (s, 3H), 4.0 (s, 3H), 7.12 (d, J_{HH} = 7.5 Hz, 2H), 7.57 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 35.6, 56.7, 60.6, 117.4, 122.6, 123.5, 124.8, 152.5, 167.1, 177.6; HRCI MS $(M)^+$ calcd. for $C_{10}H_{12}O_4$: 196.0736, found: 196.0745.

2-Bromophenylacetic acid (4j):[10]

Mp 103-105 °C (lit.[10] 103-105 °C); yield 90%; ^{1}H NMR (200 MHz, $CDCl_3$): 3.81 (s, 3H), 7.12 (m, 2H), 7.29 (d, J_{HH} = 7.8 Hz, 1H), 7.58 (d, J_{HH} = 7.8 Hz, 1H); ^{13}C NMR (50 MHz): δ 41.8, 124.1, 127.8, 129.0, 131.8, 132.6, 132.7, 177.7.

Tridecanoic acid (4k):

Yield 77%; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.90 (m, 3H); 1.20-1.40 (m, 18H), 1.63 (m, 2H), 2.36 (t, J_{HH} = 7.3 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 24.8, 29.3, 29.6, 31.9, 34.1, 177.2; HRCI MS $(M)^+$ calcd. for $C_{13}H_{26}O_2$: 214.1933, found: 214.1929.

References (Experimental):

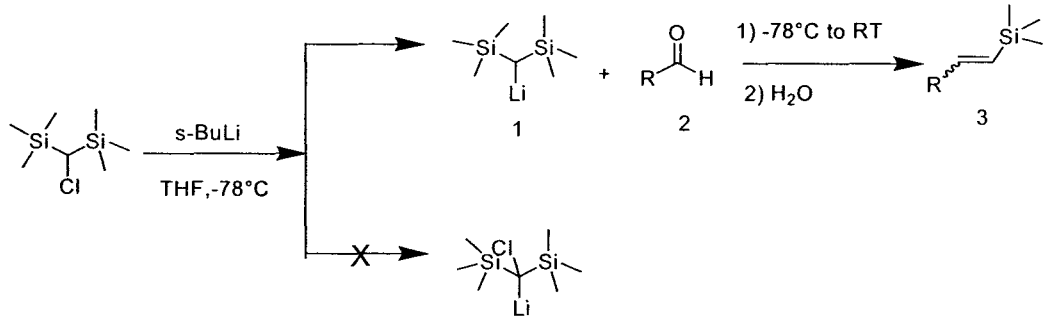
1. Moreira, D. R. M.; Lima-Leite, A. C.; Pinheiro-Ferreira, P. M.; da Costa, P, M.; Costa- Lotufo, L. V.; de Moraes, M. O.; Brondani, D. J.; Pessoca, C. O. *Eur. J. Med. Chem.* **2007**, 42, 351-357.
2. McNulty, J.; Das, P.; Gosciniak, D. *Tetrahedron Lett.* **2008**, 49, 281-285.
3. Zhou, G. B.; Zhang, P. F.; Pan, Y. J. *Tetrahedron* **2005**, 61, 5671-5677.
4. Milne, J. E.; Murry, J. A.; King, A.; Larsen, R. D. *J. Org. Chem.* **2009**, 74, 445-447.
5. Ando, A.; Miki, T.; Kumadaki, I. *J. Org. Chem.* **1988**, 53, 3637-3639.
6. Niu, D. F.; Xiao, N. L. P.; Zhang, A. J.; Zhang, G. R.; Tan, Q. Y.; Lu, J. X. *Tetrahedron* **2008**, 64, 10517-10520.
7. Li, P.; Alper, H. *J. Org. Chem.* **1986**, 51, 4354-4356.
8. Milne, J. E.; Murry, J. A.; King, A.; Larsen, R. D. *J. Org. Chem.* **2009**, 74, 445-447.
9. Chakravarti, S.; Swaminathan, M. *Ind. J. Chem.* **1934**, 11, 107-113.
10. Adamczyk, M.; Watt, D. S. *J. Org. Chem.* **1984**, 49, 4226-4237.

Chapter III

Rapid and efficient entry to vinylsilanes from aldehydes employing a novel metalation-Peterson sequence

Introduction:

Vinyl silanes have proven to be of value in a variety of useful synthetic transformations in view of the mild reactivity and controlled regioselectivity observed[1,2]. Applications of vinyl silanes in total synthesis appear to be less common, however due to the lack of a rapid general entry to this functional group. There are various methodologies available for their synthesis. Some of the important ones utilize, alkynes[3], alkenyl halides[4] and carbonyl compounds[5] as starting materials. Using carbonyl compounds seems to be the most general method for the synthesis of vinylsilanes via Peterson olefination[6] reaction. The obvious choice for this purpose is [bis(silyl)methyl]lithium as the reagent. Unfortunately, tetraalkylsilanes have shown sluggishness towards lithium-hydrogen exchange[7], unless there is an additional stabilizing effect by neighbouring heteroatom or electron-withdrawing groups[8].



Scheme 1

As a result, the yields of the addition-elimination reaction were low to moderate (25-70%)[5b]. Herein, we report a novel metal-halogen exchange mediated quantitative

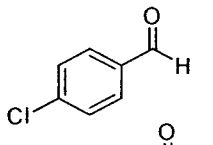
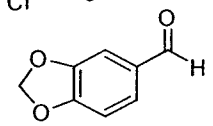
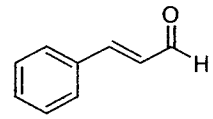
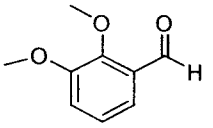
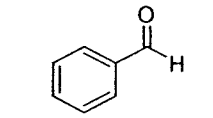
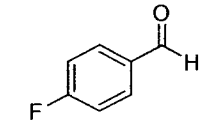
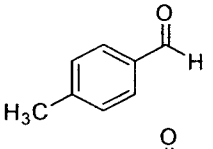
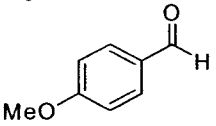
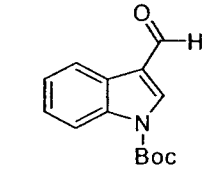
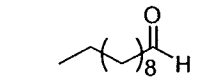
generation of [bis(trimethylsilyl)methyl]lithium from readily available bis(trimethylsilyl)chloromethane[9] followed by a Peterson reaction allowing the synthesis of vinyl silanes with high yield and good (*E*) stereoselectivity.

Results & Discussion:

The lithium reagent **1** was formed quantitavely by the lithium-chlorine exchange of bis(trimethylsilyl)chloromethane with sec-butyllithium in THF at -78°C (Scheme 1). We believe since the chloromethylene proton is hindered by the two trimethylsilyl groups, chlorine-lithium exchange took place instead of lithium-proton exchange. To the best of our knowledge, there is no report of lithium-halogen exchange from a bis-trimethylsilyl-chloromethylene group in the literature. The lithium-halogen exchange with *n*-BuLi and *t*-BuLi was unsatisfactory under the same reaction conditions. The scope of the addition-elimination reaction was investigated with a range of aromatic aldehydes and one aliphatic aldehyde, the results of which are summarized in Table 1. Yields and (*E*) stereoselectivity are good in all cases. No significant electronic effect was observed with both electron donating and electron withdrawing derivatives (entries 1 to 9) reacting equally well. Under the reaction conditions, reaction of [bis(trimethylsilyl)methyl]lithium with undecanal led to the formation of corresponding vinylsilane **3j** with 77% yield and (4:1) (*E*) stereoselectivity. It is reported that [bis(silyl)methyl]lithium reagent gives very low yield with enolizable aldehydes[5b]. One explaination of our relatively higher yield with enolizable undecanal lies in the fact that our way of generation of the reagent [bis(silyl)methyl]lithium is via a lithium-chlorine exchange, a fast process; whereas in the literature, [bis(silyl)methyl]lithium was generated via *t*-BuLi [5b] mediated proton-lithium exchange. Since it has been well documented that tetraalkylsilanes are very difficult to

deprotonate, we think that the presence of lots of unreacted *t*-BuLi in previous cases caused very low yield of the aliphatic vinylsilanes.

Table 1. Reactions of $(TMS)_2CHLi$ with aldehydes

RCHO		% yield	E/Z
	(2a)	90	> 9:1
	(2b)	95	>9:1
	(2c)	81	>9:1
	(2d)	90	>9:1
	(2e)	80	>9:1
	(2f)	85	>9:1
	(2g)	87	>9:1
	(2h)	93	>9:1
	(2i)	65	>9:1
	(2j)	77	4:1

The *trans*-olefin selectivity in the product vinylsilanes can be readily explained as follows. β-Hydroxysilanes can undergo elimination to form olefins through either a concerted *syn-periplanar* reaction pathway, typically under basic reaction conditions, or through a stepwise *anti-periplanar* pathway, typically occurring under acidic conditions.[10] Conformational analysis of the present relevant β-oxidosilane intermediate is shown, conformers A and B in Figure 1.

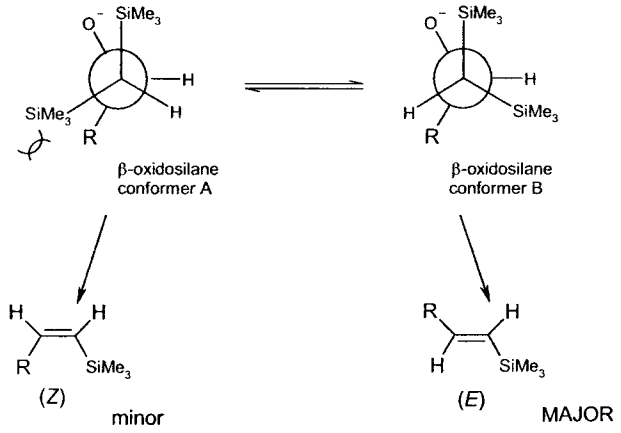


Fig. 1 Favoured *syn*-periplanar elimination from conformer B

This intermediate possesses two diastereotopic TMS groups capable of participating in the expected syn-elimination. Conformer A indicates the presence of a steric non-bonding interaction which is absent in conformer B thus favoring elimination from conformer B and leading to the (*E*)-vinylsilanes as the kinetic reaction products under these conditions.

Conclusion:

In conclusion, we have shown that bis(trimethylsilyl)chloromethane readily undergoes lithium-halogen exchange with *s*-BuLi, and that the resulting anion adds readily to aromatic, vinyl as well as enolizable aldehydes in Peterson fashion to yield vinylsilanes

in good yield and (*E*)-stereoselectivity. Further extension and application of the method is currently under investigation.

References:

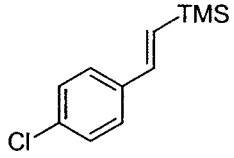
1. Fleming, I.; Barbero, I. A.; Walter, D. *Chem. Rev.* **1997**, 97, 2063-2192.
2. (a) Tsuji, J. *Palladium Reagents and Catalysts*, Wiley, Chichester, 2004, pp 335-348. (b) T. Hiyama, T.; Shirakawa, E. *Organosilicon Compounds* in Topics in Curent Chemistry, 219, Springer-Verlag, Berlin, **2002**, pp 61-85. c) T. A. Blumenkopf, T. A.; Overman, L. E. *Chem Rev.* **1986**, 86, 857-873.
3. (a) Dash, A. K.; Wang, J. Q.; Eisan, M. S. *Organometallics* **1999**, 8, 4724-4741. (b) Bratovanov, S.; Kózmínski, W.; Fässler, J.; Molnar, Z.; Nanz, D.; Bienz, S. *Organometallics* **1997**, 16, 3128-3134. (c) Asao , N.; Sudo, T.; Yamamoto, Y. *J. Org. Chem.* **1996**, 61, 7654-7655. (d) Mitchell, T. N.; Wickenkamp, R.; Amamria, A.; Dicke, R.; Schneider, U. *J. Org. Chem.* **1987**, 52, 4868-4874.
4. (a) Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* **1999**, 40, 9255-9257. (b) Fugami, K.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1986**, 27, 2161-2164.
5. (a) Seebach, D.; Bürstinghaus, R.; Gröbel, B. T.; Kolb, M. *Liebigs Ann. Chem.* **1977**, 830-845. (b) Gröbel, B. T.; Seebach, D. *Chem. Ber.* **1977**, 110, 852-866. (c) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, 3465-3468. (d) Fleming, I.; Pearce, A. *J. Chem. Soc., Perkin Trans. 1,* **1980**, 2485-2489. (e) Carter, M. J.; Fleming, I.; Percival, A. *J. Chem. Soc., Perkin Trans. 1,* **1981**, 2415-2434. (f) Sato, Y.; Takeuchi, S. *Synthesis* **1983**, 734-735. (g) Ager, D. J. *J. Org. Chem.* **1984**, 49, 168-170. (f) Sato, Y.; Takeuchi, S. *Synthesis* **1983**, 734-

735. (g) Ager, D. J. *J. Org. Chem.* **1984**, 49, 168-170. (h) Takeda, T.; Ando, K.; Mamada, A.; Fujiwara, T. *Chem. Lett.* **1985**, 1149-1152. (i) R. K Boeckman. R.; K. Jr.; Chinn, R. L. *Tetrahedron Lett.* **1985**, 26, 5005-5008. (j) Ager, D. J.; East, M. B. *J. Org. Chem.* **1986**, 51, 3983-3992. (k) Williams, D. R.; Morales-Ramos, A. I.; Williams, C. M. *Org. Lett.* **2006**, 8, 4393-4396. (l) Balazs, L.; Breunig, H. J.; Ghesner, I.; Lork, E. *J. Organomet. Chem.* **2002**, 648, 33-38.

6. Peterson, D. J. *J. Org. Chem.* **1968**, 33, 780-784.
7. Peterson, D. J. *J. Organomet. Chem.* **1967**, 9, 373-374.
8. (a) Gornowicz, G. A.; West, R. *J. Am. Chem. Soc.* **1968**, 90, 4478-4479. (b) Brook, M.A. Silicon in Organic, Organometallic, and Polymer Chemistry; John Wiley & Sons: New York, **2000**. (c) Colvin, E. W. Silicon Reagents in Organic Synthesis; Academic Press: London, **1988**. (d) Weber, W. P. Silicon Reagents for Organic Synthesis; Springer- Verlag: Berlin, **1983**.
9. (a) Itami, K.; Nokami. T.; Yoshida, J. *Org. Lett.* **2000**, 2, 1299-1302. (b) M.L. Kwan, M. L.; Yeung, C. W.; Breno, K. L.; Doxsee, K. M. *Tetrahedron Lett.* **2001**, 42, 1411-1414. (c) Concellon, J. M.; Bernard, P. L.; Bardales, E. *Org. Lett.* 2**001**, 3, 937-939.
10. This reagent is available from the Aldrich Chemical Company.
11. Hudrlik, F. P.; Agwaramgbo, E. L. O.; Hudrlik, M. A. *J. Org. Chem.* **1989**, 54, 5613-5618.

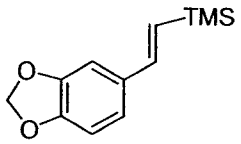
Experimental:

(*E*)-4-Chlorostyryl-trimethylsilane [1](3a):



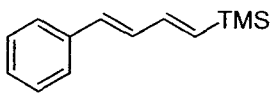
Into a flame-dried flask, containing a magnetic stirring bar, was weighed bis(trimethylsilyl)chloromethane (100 μL, 0.459 mmol) under argon and dry THF (918 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (426 μL, 0.596 mmol, 1.4M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of 4-chlorobenzaldehyde (77.4 mg, 0.551 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The starting material was separated from the product using silica gel column chromatography and eluted with 10% ethyl acetate in hexane to yield **3a,** 87 mg, (90%) as colorless viscous oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.14 (s, 9H), 6.47 (d, 1H, J_{HH} = 19.1 Hz), 6.80 (d, 1H, J_{HH} = 19.1 Hz), 7.34 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ -1.1, 127.5, 128.6, 130.4, 133.2, 136.9, 142.1; HRMS $(M)^+$ calcd. for $C_{11}H_{15}ClSi$: 210.0631, found: 210.0632.

(*E*)-4-(3',4'-Methylenedioxy)styryltrimethylsilane [2](3b):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed bis(trimethylsilyl)chloromethane (100 μL, 0.459 mmol) under argon and dry THF (918 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (426 μL, 0.596 mmol, 1.4M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of piperonal (82.7 mg, 0.551 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The starting material was separated from the product using silica gel column chromatography eluted with 10% ethyl acetate in hexane to yield **3b,** 96 mg, (95%) as off white viscous oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.15 (s, 9H), 5.91 (s, 2H), 6.23 (d, J_{HH} = 19 Hz, 1H), 6.73 (d, J_{HH} = 19 Hz, 1H), 6.71-7.22 (m, 3H); HRMS $(M)^+$ calcd. for $C_{12}H_{16}O_2Si$: 220.0933, found: 220.0920.

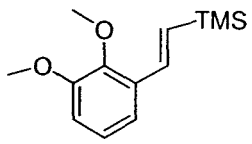
Trimethyl((1*E*,3*E*)-4-phenylbuta-1,3-dienyl)silane[3] (3c):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed bis(trimethylsilyl)chloromethane (100 μL, 0.459 mmol) under argon and dry THF (918 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (426 μL, 0.596 mmol, 1.4M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of trans-cinnamaldehyde (69.5 μL, 0.551 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting

mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The starting material was separated from the product using silica gel column chromatography eluted with 10% ethyl acetate in hexane to yield **3c,** 75.2 mg, (81%) as semisolid.^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.12 (s, 9H), 6.02 (d, J_{HH} = 18.1 Hz, 1H), 6.58 (d, J_{HH} = 15.4 Hz, 1H), 6.69 (dd, J_{HH} = 10.1 Hz, 18.1 Hz, 1H), 6.79 (dd, J_{HH} = 10.1 Hz, 18.1 Hz, 1H), 7.20-7.45 (m, 5H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ -1.0, 126.7, 127.8, 128.6, 131.8, 133.0, 135.2, 137.2, 144.2; HRMS $(M)^+$ calcd. for $C_{11}H_{18}Si$: 202.1179, found: 202.1178.

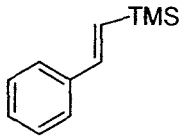
(*E*)-2,3-Dimethoxystyryltrimethylsilane (3d):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed bis(trimethylsilyl)chloromethane (100 µL, 0.459 mmol) under argon and dry THF (918 µL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (426 µL, 0.596 mmol, 1.4M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of 2,3-dimethoxybenzaldehyde (91.6 mg, 0.551 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The starting material was separated from the product using silica gel column chromatography eluted

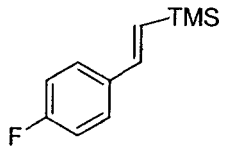
with 10% ethyl acetate in hexane to yield **3d,** 97.6 mg, (90%) as semisolid.^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.17 (s, 9H), 3.80 (s, 3H), 3.87 (s, 3H), 6.47 (d, J_{HH} = 19.4 Hz, 1H), 6.81 (d, J_{HH} = 9.4 Hz, 1H), 7.02 (t, J_{HH} = 8.01 Hz, 1H), 7.17 (d, J_{HH} = 9.4 Hz, 1H), 7.25 (d, J_{HH} = 19.4 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ -1.1, 55.9, 61.1, 111.7, 117.8, 124.0, 131.1, 132.7, 137.5, 146.5, 152.5; HRMS $(M)^+$ calcd. for $C_{13}H_{20}O_2Si$: 236.1249, found: 236.1233.

(*E*)-Styryltrimethylsilane [4] (3e):



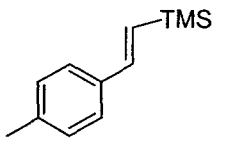
Into a flame-dried flask, containing a magnetic stirring bar, was weighed bis(trimethylsilyl)chloromethane (100 µL, 0.459 mmol) under argon and dry THF (918 µL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (426 µL, 0.596 mmol, 1.4M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of benzaldehyde (56 µL, 0.551 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 hrs and then slowly warmed to room temperature where it was stirred for a further 2 hr. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The starting material was separated from the product using silica gel column chromatography eluted with 10% ethyl acetate in hexane to yield **3e,** 75.78 mg, (80%) as colorless viscous oil.^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.16 (s, 9H), 6.47 (d, J_{HH} = 19.4 Hz, 1H), 6.86 (d, J_{HH} = 19.4 Hz, 1H), 7.17-7.41 (m, 5H); HRMS $(M)^+$ calcd. for $C_{11}H_{16}Si$: 176.1015, found: 176.1021.

(*E*)-4-Fluorostyryltrimethylsilane [4](3f):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed bis(trimethylsilyl)chloromethane (100 μL, 0.459 mmol) under argon and dry THF (918μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (426 μL, 0.596 mmol, 1.4M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of 4-fluorobenzaldehyde (59.1 μL, 0.551 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The starting material was separated from the product using silica gel column chromatography eluted with 10% ethyl acetate in hexane to yield **3f,** 75.76 mg, (85%) as viscous oil.^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.15 (s, 9H), 6.37 (d, J J_{HH} = 19.5 Hz, 1H), 6.82 (d, J_{HH} = 19.5 Hz, 1H), 7.02-7.40 (m, 4H); HRMS $(M)^+$ calcd. for $C_{11}H_{15}FSi$: 194.0926, found: 194.0927.

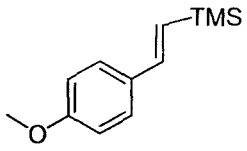
(*E*)-4-Methylstyryltrimethylsilane [4](3g):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed bis(trimethylsilyl)chloromethane (100 μL, 0.459 mmol) under argon and dry THF (918

μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (426 μL, 0.596 mmol, 1.4M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of 4-methylbenzaldehyde (65 μL, 0.551 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The starting material was separated from the product using silica gel column chromatography eluted with 10% ethyl acetate in hexane to yield **3g,** 75.96 mg, (87%) as viscous oil.^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.15 (s, 9H), 2.57 (s, 3H), 6.37 (d, J_{HH} = 19.5 Hz, 1H), 6.82 (d, J_{HH} = 19.5 Hz, 1H), 7.02-7.40 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ -1.0, 21.5, 126.1, 128.9, 129.7, 135.2, 137.1, 143.6; HRMS $(M)^+$ calcd. for $C_{12}H_{18}Si$: 190.1176, found: 190.1178.

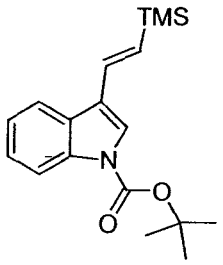
(*E*)-4-Methoxystyryltrimethylsilane [2] (3h):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed bis(trimethylsilyl)chloromethane (100 μL, 0.459 mmol) under argon and dry THF (918μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (426 μL, 0.596 mmol, 1.4M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of 4-methoxybenzaldehyde (67 μL, 0.551 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting

mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The starting material was separated from the product using silica gel column chromatography eluted with 10% ethyl acetate in hexane to yield **3h,** 88.03 mg, (93%) as viscous oil.^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.11 (s, 9H), 3.77 (s, 3H), 6.27 (d, J_{HH} = 19.1 Hz, 1H), 6.81 (d, J_{HH} = 19.1 Hz, 1H), 6.84 (d, J_{HH} = 9 Hz, 2H), 7.33 (d, J= 9 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ -1.11, 56.5, 113.2, 127.1, 127.8, 131.7, 143.1, 159.6; HRMS $(M)^+$ calcd. for $C_{12}H_{18}OSi$: 206.1121, found: 206.1127.

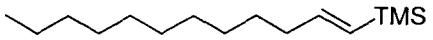
t-butyl 3-(*E*)-2-(trimethylsilyl)vinyl)-1H-indole-1-carboxylate (3i):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed bis(trimethylsilyl)chloromethane (100 μL, 0.459 mmol) under argon and dry THF (918μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon sec-BuLi (426 μL, 0.596 mmol, 1.4M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of tert-butyl 3-formyl-1H-indole-1-carboxylate (119.7 mg, 0.551 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane

(3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The starting material was separated from the product using silica gel column chromatography eluted with 10% ethyl acetate in hexane to yield **3i,** 94.06 mg, (65%) as yellow semisolid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.18 (s, 9H), 1.67 (s, 9H), 6.52 (d, J_{HH} = 19.3 Hz, 1H), 7.01 (d, J_{HH} = 19.3 Hz, 1H), 7.21-7.41 (m, 2H), 7.66 (s, 1H), 7.89 (d, J_{HH} = 7.96 Hz, 1H), 8.18 (d, J_{HH} = 7.96 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ -1.12, 19.7, 84.5, 115.5, 120.2, 120.7, 123.1, 124.3, 124.8, 128.9, 130.2, 135.1, 136.3, 149.8; HRMS $(M)^+$ calcd. for $C_{18}H_{25}NO_2Si$ 315.1664, found: 315.1655.

(*E*)-1-Dodecenyltrimethylsilane [5] (3j):



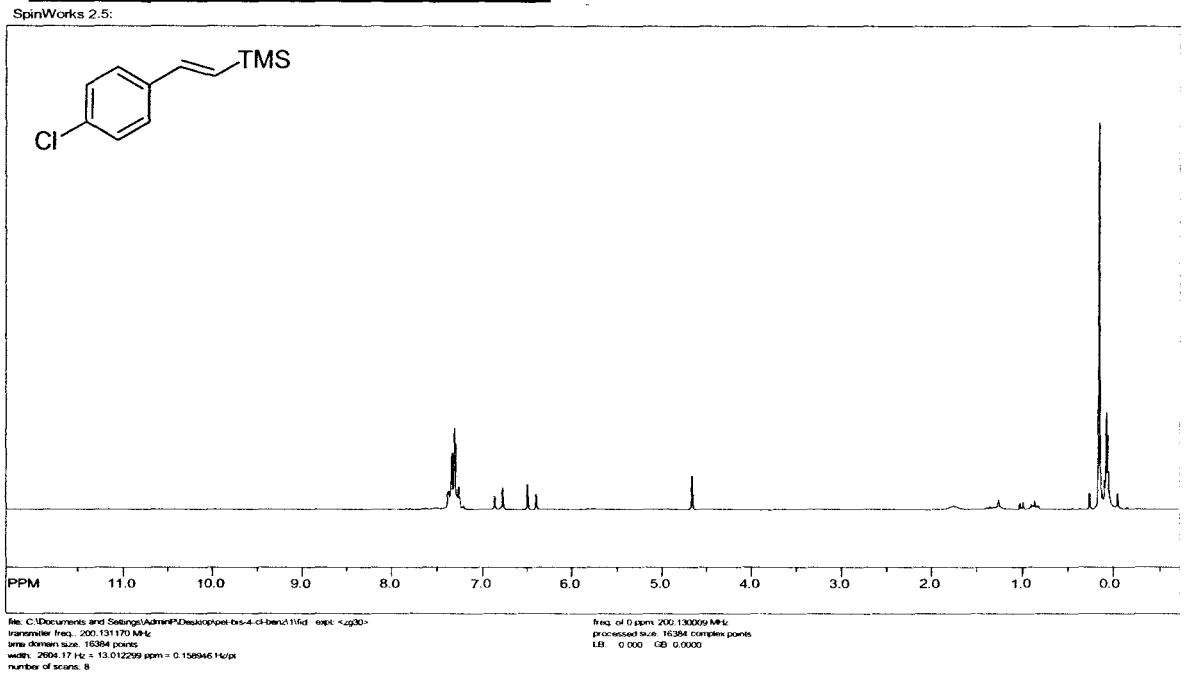
Into a flame-dried flask, containing a magnetic stirring bar, was weighed bis(trimethylsilyl)chloromethane (100 μL, 0.459 mmol) under argon and dry THF (918 μL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (426 μL, 0.596 mmol, 1.4M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of undecanal (113.7 μL, 0.551 mmol) was added slowly to the reaction flask at -78°C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3X15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The starting material was separated from the product using silica gel column chromatography eluted with 10% ethyl acetate in hexane to yield **3j,** 84.94 mg, (77%) as colorless oil.^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 9H), 0.88 (m, 3H), 1.20-1.44 (m, 16H), 2.09 (m, 2H), 5.61(dt, J_{HH} =

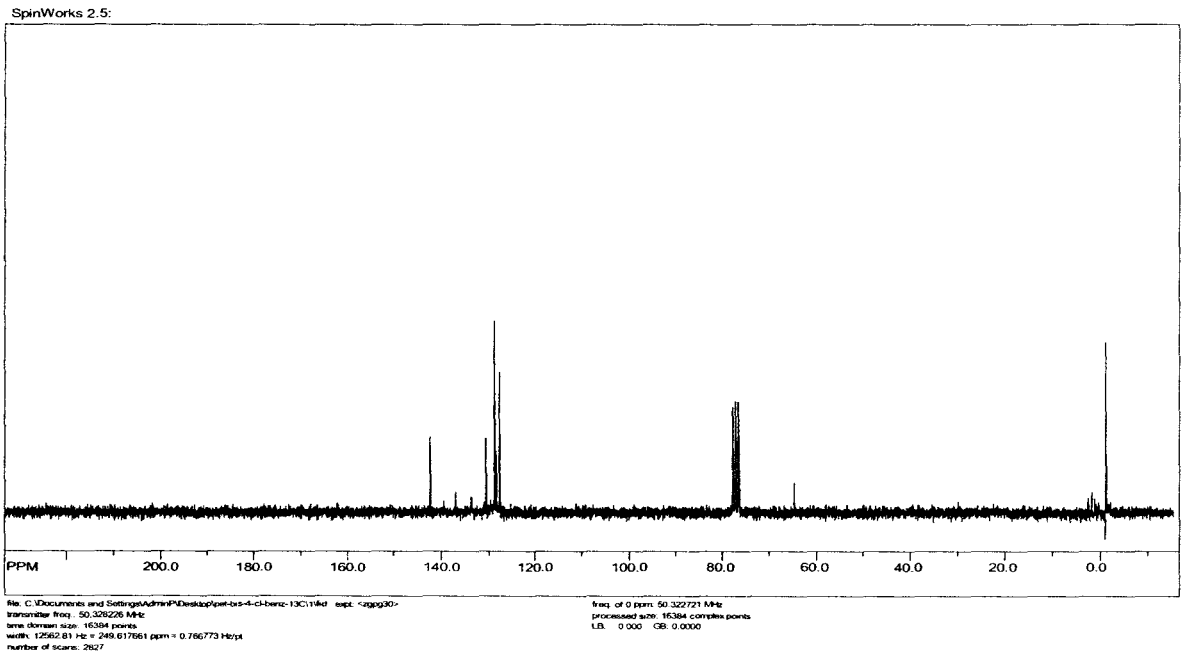
1.5 Hz, 18.2 Hz, 1H), 6.02 (dt, J_{HH} = 6.3 Hz, 18.2 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ -1.12, 14.1, 22.6, 28.6, 29.1, 29.4, 24.5, 29.62, 29.63, 31.8, 36.8, 129.3, 147.4; HRMS $(M)^+$ calcd. for $C_{15}H_{32}Si$: 240.2289, found: 240.2273.

References (Experimental):

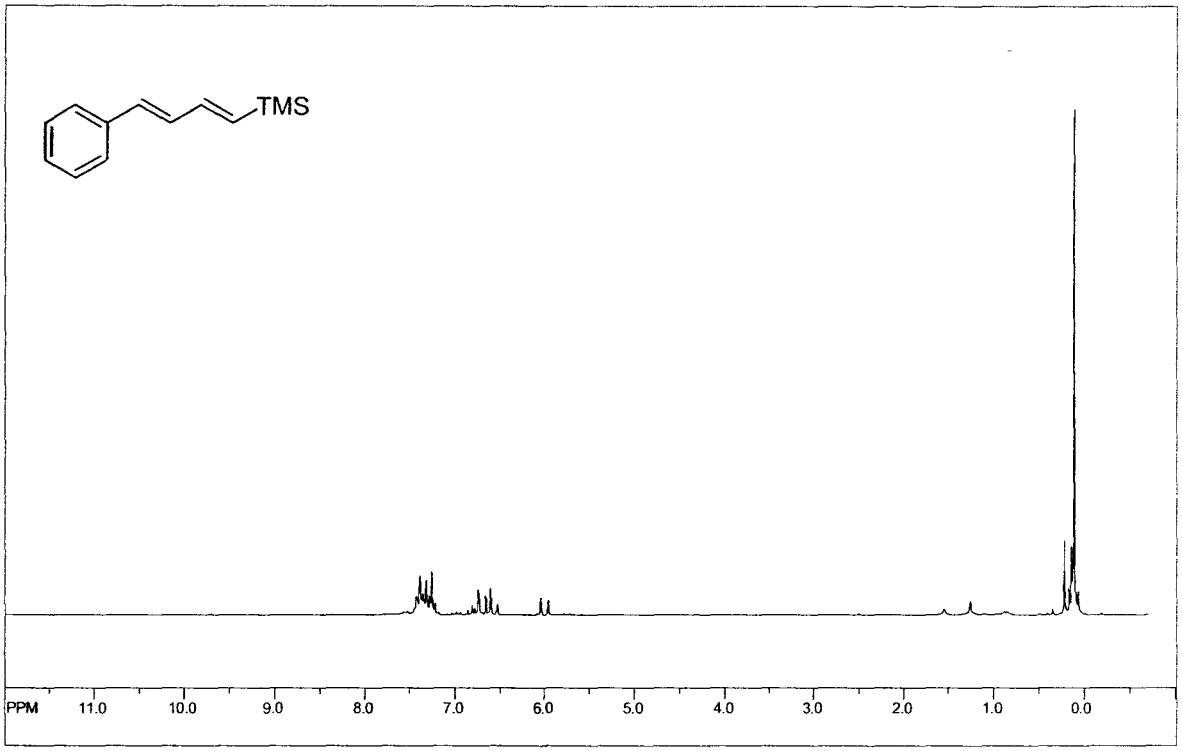
1. Nakano, T.; Miyamoto, T.; Endoh, T.; Shimotani, M.; Ashida, N.; Morioka, T Takahashi, Y. *Appl. Organomet. Chem.* **2004**, 18, 65-67.
2. Zhi-Jie, N.; Pin-Fan, Y.; Dennia, N. P. K.; Yih-Ling, T.; Tien-Yau, L. *J. Am. Chem. Soc.* **1990**, 112, 9356-9364.
3. Francesco, B.; Gianluca, M. F.; Franscesco, N.; Daniela, P. *J. Org. Chem.* **2000**, 65, 1554-1557.
4. Wang, C.; Yan, L.; Zhiguo, Z.; Yang, D.; Pan, Y. *Tetrahedron* **2006**, 62, 7712-7717.
5. Kenichiro, I.; Koji, T.; Jun-Chi, Y.; Okitsugu, K. *J. Am. Chem. Soc.* **2003**, 125, 6058-6059.

NMR Spectra of New Compounds:





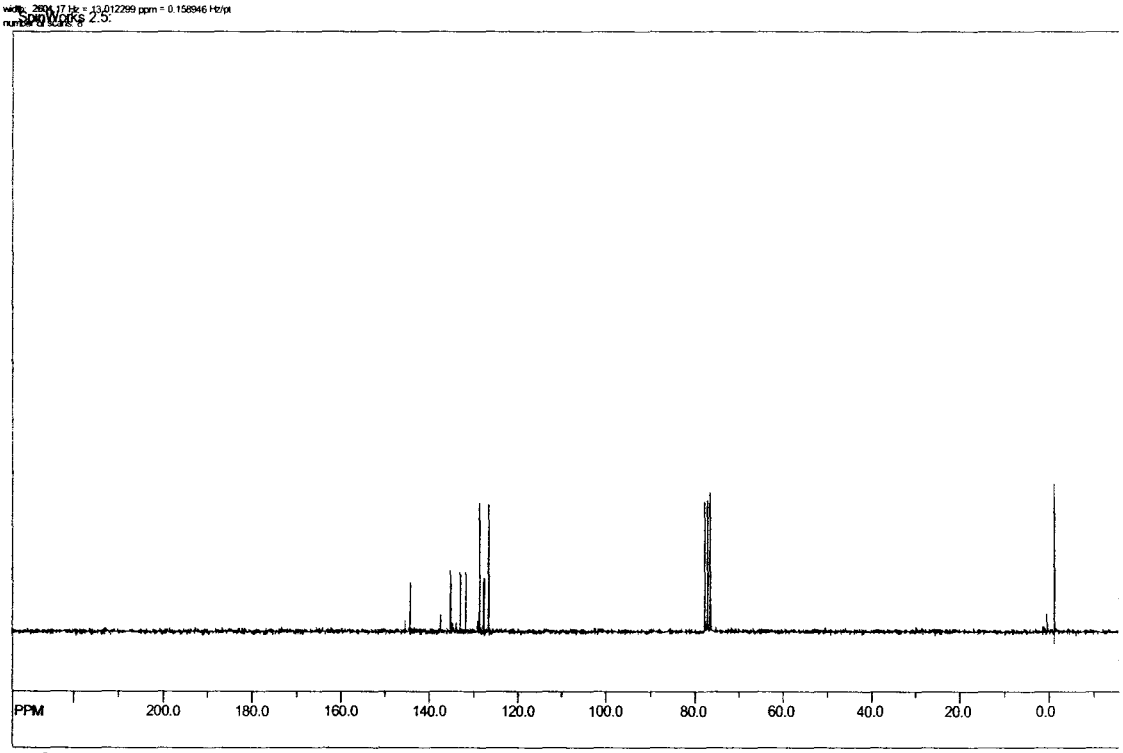
SpinWorks 2.5:



file: C:\Documents and Settings\AdminP\Desktop\pet-trans-cinamal-vinyl-TMS\1\fid expt: <zg30>
transmitter freq.: 200.131170 MHz
time domain size: 16384 points
width: 2894.17 Hz = 13.012299 ppm = 0.158946 Hz/pt
number of scans: 8

freq. of 0 ppm: 200.130009 MHz
processed size: 16384 complex points
LB: 0.000 GB: 0.0000

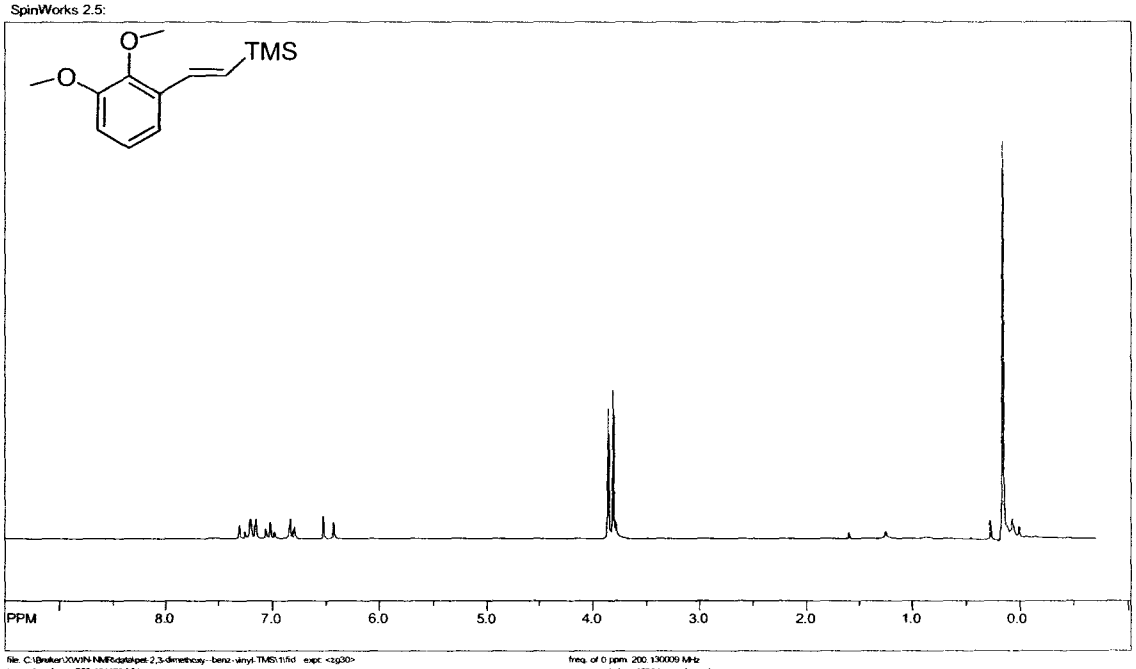
SpinWorks 2.5:



file: C:\Documents and Settings\AdminP\Desktop\pet-trans-cinamal-vinyl-TMS\2\fid expt: <zgpg30>
transmitter freq.: 50.328226 MHz
time domain size: 16384 points
width: 12562.81 Hz = 249.617661 ppm = 0.766773 Hz/pt
number of scans: 4500

freq. of 0 ppm: 50.322724 MHz
processed size: 16384 complex points
LB: 0.000 GB: 0.0000

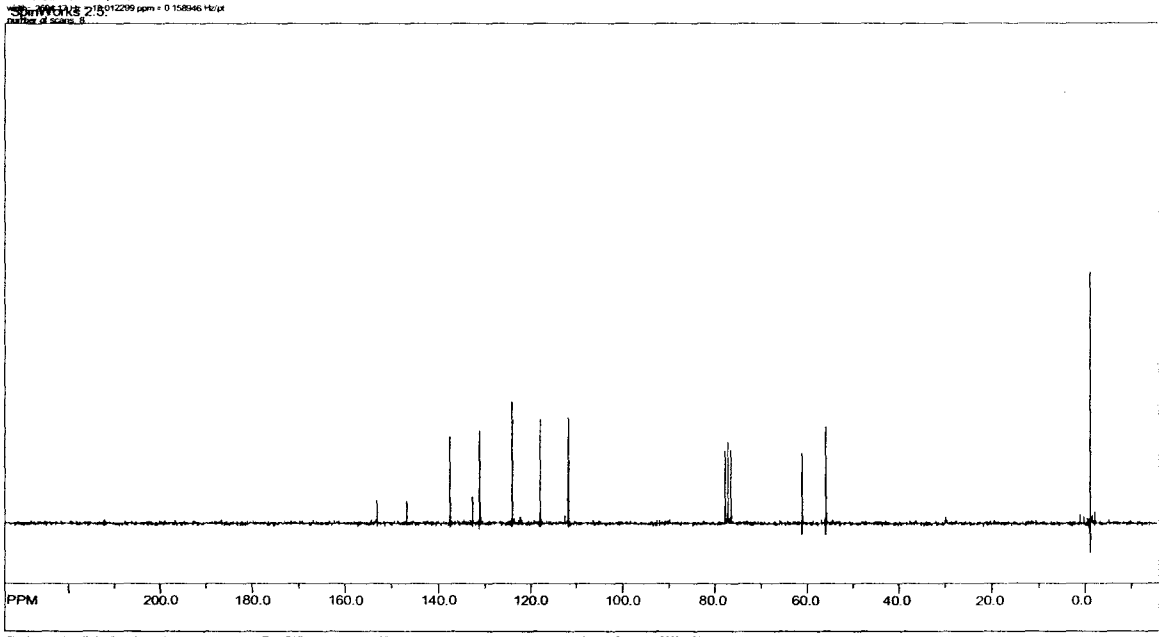
SpinWorks 2.5:



file: C:\Bruker\XWIN-NMR\data\pst-2,3-dimethoxy--benz-vinyl-TMS\1\1\fid expc <zg30>
transmitter freq.: 200.131170 MHz
time domain size: 16384 points
width: 4004.01 Hz = 20.012299 ppm = 0.158946 Hz/pt
number of scans: 8

freq. of 0 ppm: 200.130009 MHz
processed size: 16384 complex points
LB: 0.000 GB: 0.0000

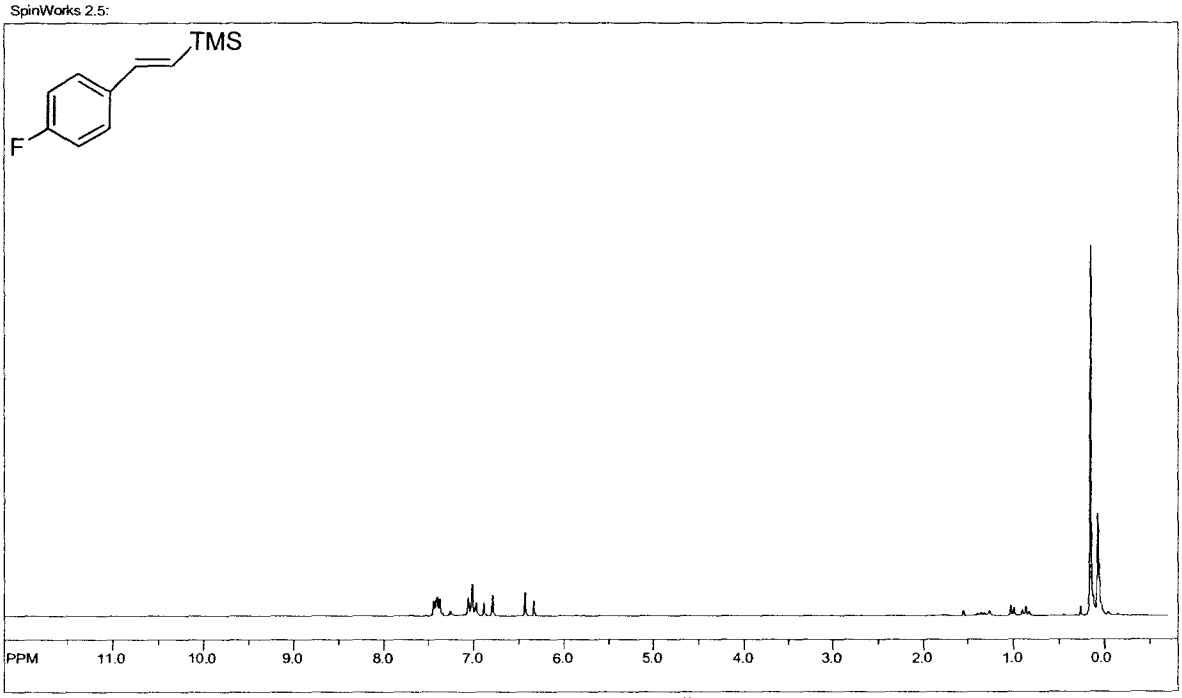
SpinWorks 2.5:



file: C:\Bruker\XWIN-NMR\data\pst-2,3-dimethoxy--benz-vinyl-TMS-C13\1\1\fid expt: <zgpg30>
transmitter freq.: 50.328226 MHz
time domain size: 16384 points
width: 12562.81 Hz = 249.617661 ppm = 0.766773 Hz/pt
number of scans: 2500

freq. of 0 ppm: 50.322727 MHz
processed size: 16384 complex points
LB: 0.000 GB: 0.0000

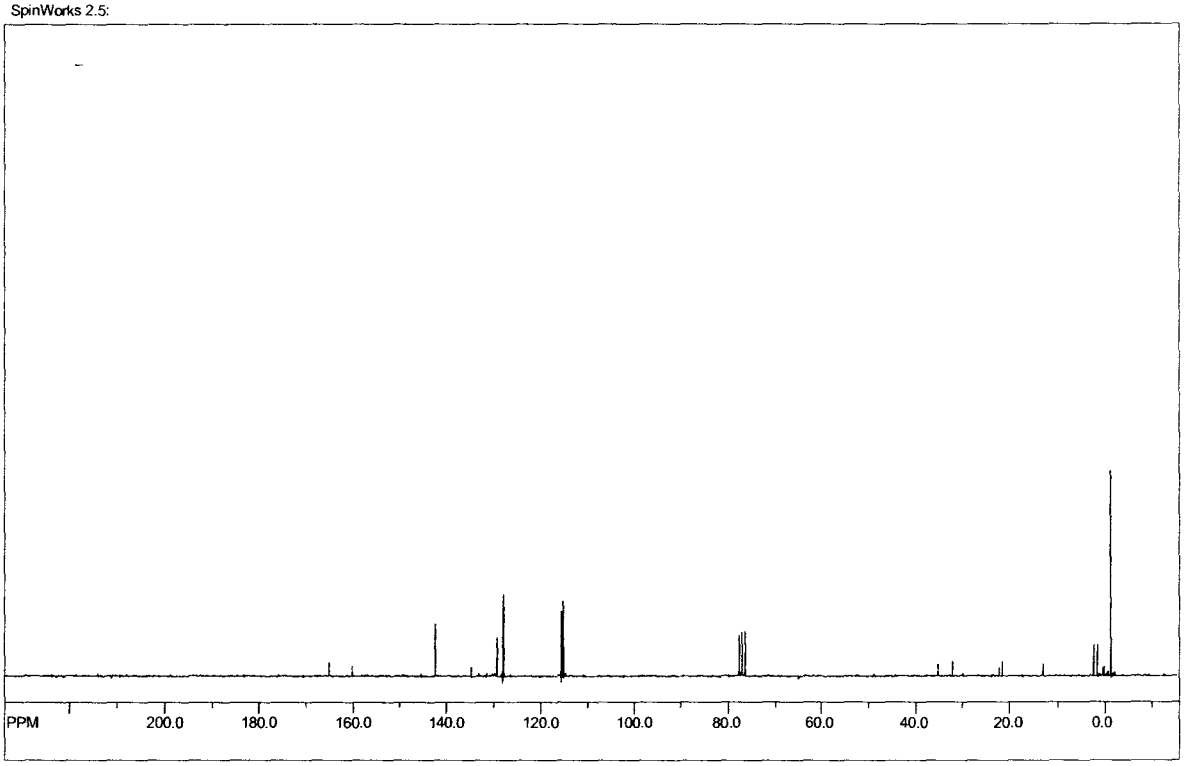
SpinWorks 2.5:



file: C:\Documents and Settings\Admin\Desktop\4-F-vinyl-silane\1\fid expt: <zg30>
transmitter freq.: 200.131170 MHz
time domain size: 16384 points
width: 2604.17 Hz = 13.012299 ppm = 0.158946 Hz/pt
number of scans: 8

freq. of 0 ppm: 200.130009 MHz
processed size: 16384 complex points
LB: 0.000 GB: 0.0000

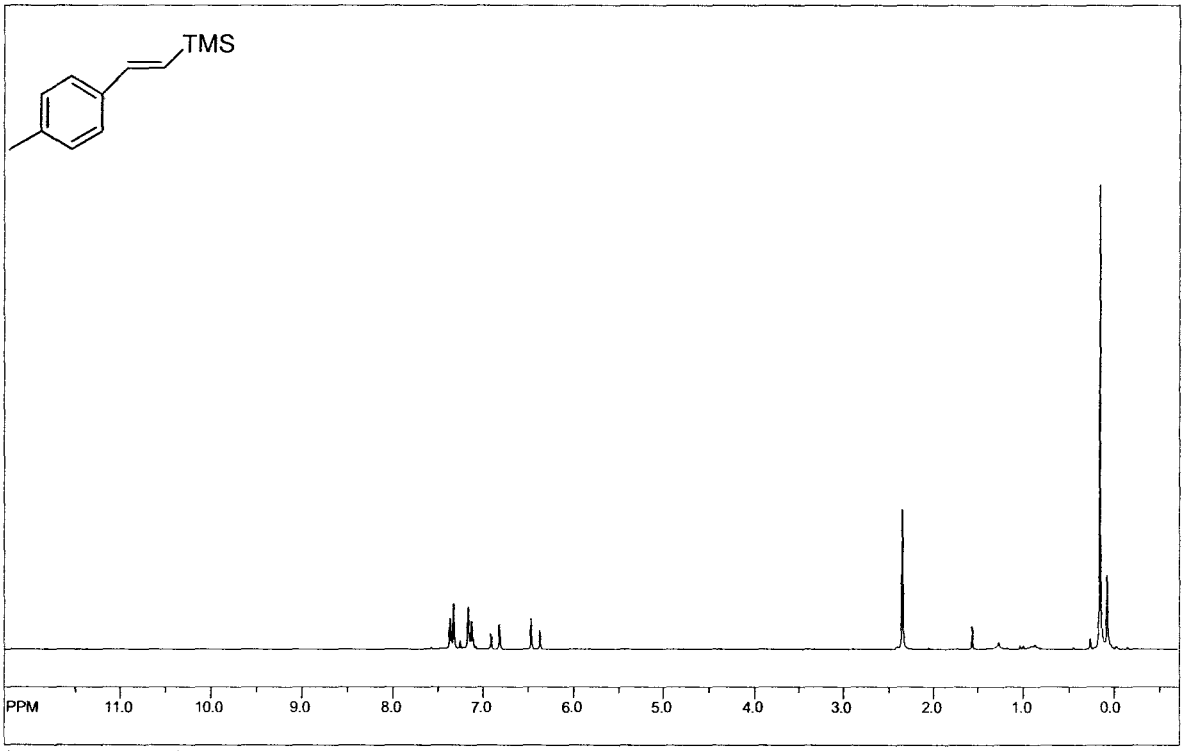
SpinWorks 2.5:



file: C:\Documents and Settings\Admin\Desktop\4-F-vinyl-silane\2\fid expt: <zgpg30>
transmitter freq.: 50.328226 MHz
time domain size: 16384 points
width: 12562.81 Hz = 249.617661 ppm = 0.766773 Hz/pt
number of scans: 1850

freq. of 0 ppm: 50.322728 MHz
processed size: 16384 complex points
LB: 0.000 GB: 0.0000

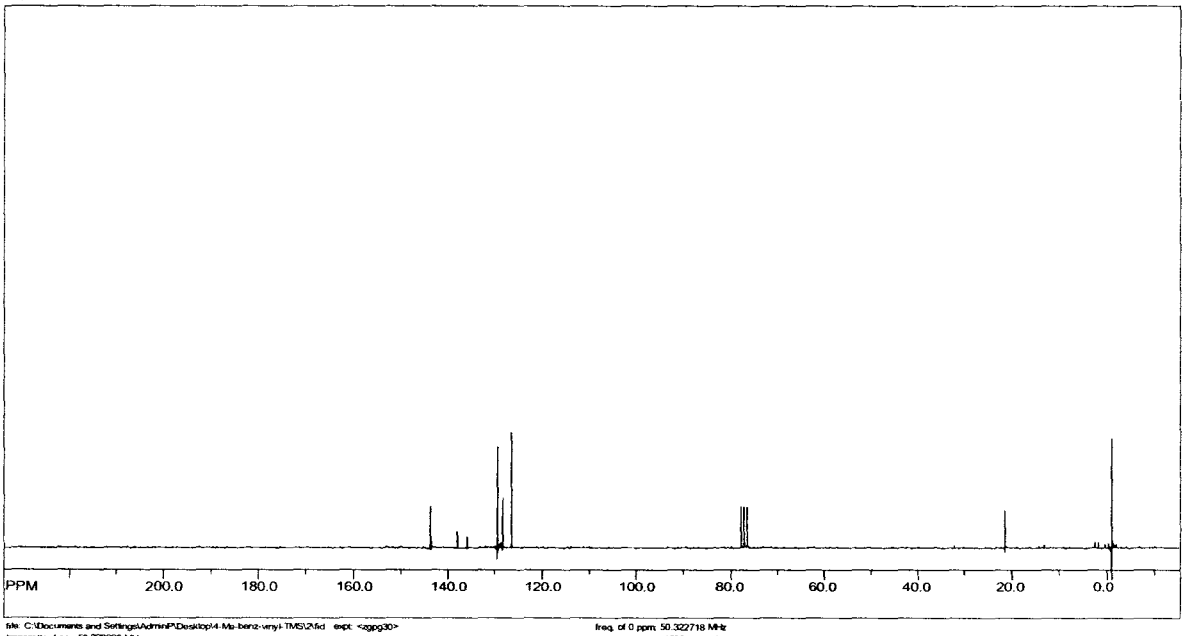
SpinWorks 2.5:



file: C:\Documents and Settings\AdminP\Desktop\4-Me-benz-vinyl-TMS\1\fid expt: <zg30>
transmitter freq.: 200.131170 MHz
time domain size: 16384 points
width: 2604.17 Hz = 13.012299 ppm = 0.158946 Hz/pt
number of scans: 8

freq. of 0 ppm: 200.130009 MHz
processed size: 16384 complex points
LB: 0.000 GB: 0.0000

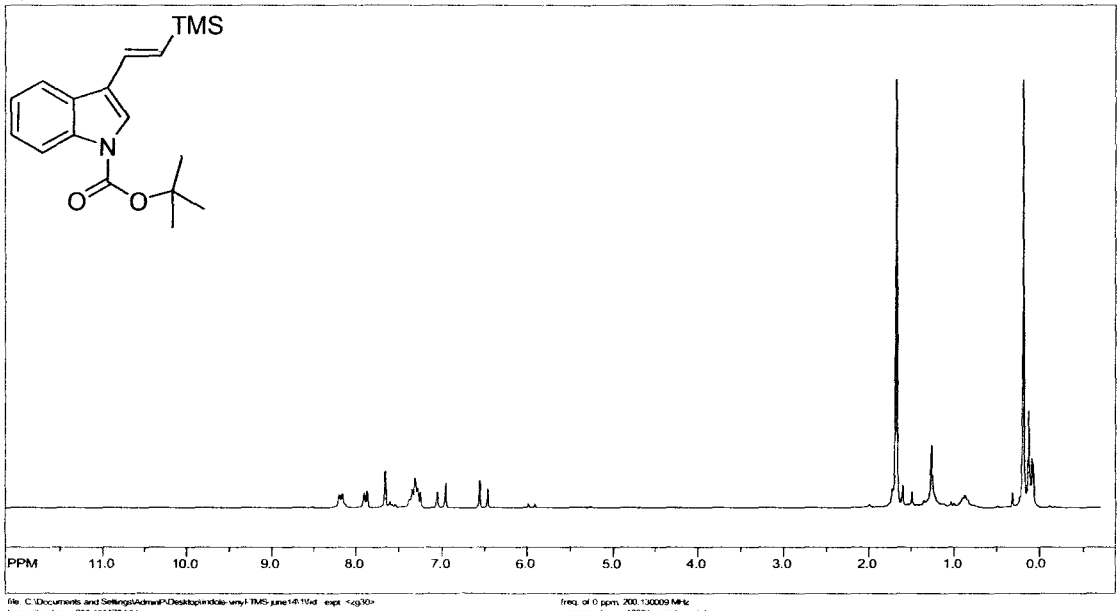
SpinWorks 2.5:



file: C:\Documents and Settings\AdminP\Desktop\4-Me-benz-vinyl-TMS\2\fid expt: <zgpg30>
transmitter freq.: 50.328226 MHz
time domain size: 16384 points
width: 12562.81 Hz = 249.617661 ppm = 0.766773 Hz/pt
number of scans: 3375

freq. of 0 ppm: 50.322718 MHz
processed size: 16384 complex points
LB: 0.000 GB: 0.0000

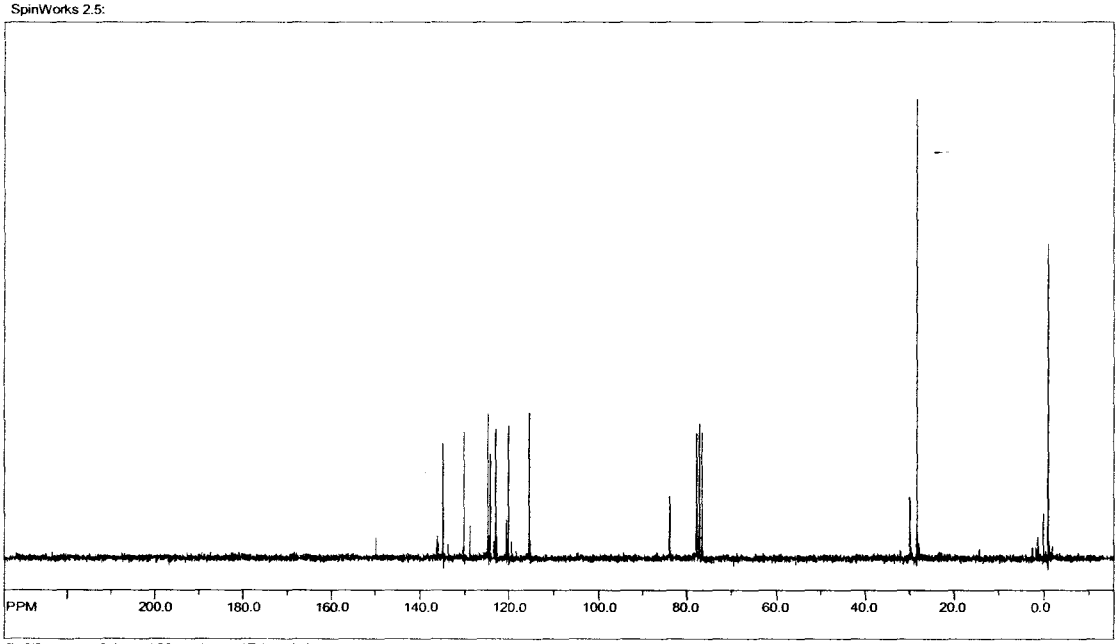
SpinWorks 2.5:



file: C:\Documents and Settings\Admin\P\Desktop\indole-vinyl-TMS-june14\1\1\fid expt: <zg30>
transmitter freq.: 200.131170 MHz
time domain size: 16384 points
width: 2604.17 Hz = 13.012299 ppm = 0.158946 Hz/pt
number of scans: 8

freq. of 0 ppm: 200.130009 MHz
processed size: 16384 complex points
LB: 0.000 GB: 0.0000

SpinWorks 2.5:



file: C:\Documents and Settings\Admin\P\Desktop\indole-vinyl-TMS-june14\2\1\fid expt: <zgpg30>
transmitter freq.: 50.326226 MHz
time domain size: 16384 points
width: 12562.81 Hz = 249.617661 ppm = 0.766773 Hz/pt
number of scans: 2912

freq. of 0 ppm: 50.322721 MHz
processed size: 16384 complex points
LB: 0.000 GB: 0.0000

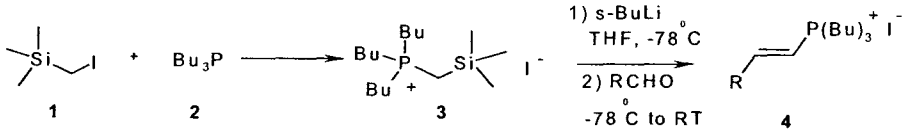
Chapter IV

A direct synthesis of vinylphosphonium salts from alpha-trimethylsilyl ylidies and non-enolizable aldehydes

Introduction:

Although the first reported synthesis of a vinylphosphonium salt **4** appeared almost 1.5 centuries ago,[1] their utility as synthetic intermediates awaited a flurry of publications in the mid-1960's.[2-4] The electrophilic nature of the olefin in such species was demonstrated through the conjugate addition of phenyllithium[2] and a range of simple nucleophiles derived from enolizable precursors and amines.[3] Conjugate addition to vinylphosphonium salts leads to an initial phosphorane (ylide) which may be subsequently trapped through an intra- or intermolecular olefination reaction. Schweizer and co-workers expanded the scope of vinylphosphonium salts to a range of conjugate addition-trapping reactions.[4] The use of this electron deficient olefin as a dienophile in Diels-Alder and other cycloaddition reactions has also been demonstrated.[3] Surprisingly, few reports on synthetic applications of vinylphosphonium salts have appeared in the literature since.[5] The synthesis of vinylphosphonium salts is usually accomplished through quaternization of a trialkyl- or triarylphosphane with a bromoethane derivative containing a β–leaving group, the olefin being introduced through a subsequent elimination step. The tetravinylphosphonium[6] cation was recently reported through a similar pathway from phosphine (PH_3). Triarylvinylphosphonium salts have also been reported *via* Pd-mediated phosphination of vinyl bromides and triflates,[7] Pd-mediated alkyne addition[8] and *via* an electrochemical oxidation process.[9] Thus, synthesis of vinylphosphonium salts requires the prior assembly of a corresponding vinyl bromide or vinyl triflate, an alkylating agent containing an

appropriate β–leaving group or a functionalized alkyne. The limitation in routes available for the synthesis of vinylphosphonium salts is arguably the major hindrance to their more widespread use, given the range of valuable synthetic interconversions that have been demonstrated.

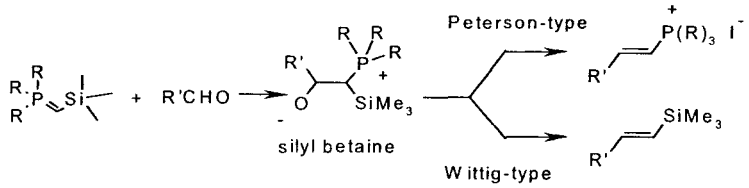


Scheme 1

Results & Discussion:

We have recently become interested in the synthesis and reactivity of bis-heteromethylenes[10] and methines[11] as a route to useful synthetic intermediates through olefination reactions with readily available carbonyl compounds. An alternative route towards the synthesis of vinylphosphonium salts might potentially be the reaction between an α–silylated ylide and carbonyl compound, as outlined in Scheme 2. The intermediate, here shown as the silyl betaine, could potentially eliminate in Peterson fashion through *O*-silyl migration yielding a vinylphosphonium salt, or alternatively through Wittig-type elimination of phosphane oxide from the betaine (or oxaphosphetane) yielding a vinylsilane. While α-trimethylsilyl ylides are well known,[12] their reactions with carbonyl compounds are reported to be complex,[13] yielding allenes[12a,13b] and many side products. Furthermore, the one example[13] of a straightforward olefination with an α-silyl ylide reacting with benzaldehyde is reported to give the vinylsilane product in good yield, a result that has been claimed to be general.[13c] On the basis of these reports, the direct synthesis of vinylphosphonium salts from α–silyl ylides and carbonyl compounds would not appear promising. Nonetheless, these results

appeared unusual to us for several reasons. First of all, we have previously observed very high chemoselectivity favouring Peterson-type elimination over Horner-Emmons phosphonate elimination with α–silyl phosphonate/aldehyde intermediates.[11] Secondly, Gilman initially postulated a vinylphosphonium intermediate in such a reaction (although it was not isolated) and showed that vinylphosphonium salts could independently be converted to allenes, the main products of Gilman's investigation.[12a] We have reinvestigated this chemistry, as shown in Scheme 2, and herein report the finding that α–silyl ylides react with aldehydes to provide vinylphosphonium salts in high yield. Commercially available[14] iodomethyltrimethylsilane **1** selectively reacts with tributylphosphine **2** yielding the α-trimethylsilylphosphonium salt **3**. The ylide derived from **3** enters into Peterson-type olefination reactions with aldehydes with high selectivity providing a direct, general synthesis of tributyl(vinyl)phosphonium salts **4**.



Scheme 2. Synthesis of vinylsilanes and/or vinylphosphonium salts *via* the reaction of an aldehyde with an α–silyl ylide.

The reaction of chloromethyltrimethylsilane with triphenylphosphine or tributylphosphine **2**, proceeded in THF to provide a mixture of the phosphonium chloride corresponding to **3** and tributyl(methyl)phosphonium chloride.[15] Desilylation reactions are characteristic in many of the α-silyl ylide preparations described above,[12a,12b,12d] produced *via* chloride mediated desilylation and protonation of the intermediate ylide. We first found that the corresponding iodide salt **3** can be formed (ICH_2TMS, Bu_3P,

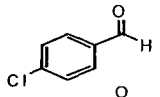
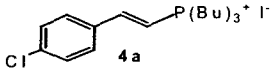
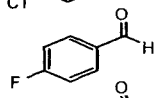
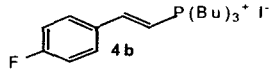
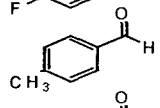
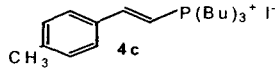
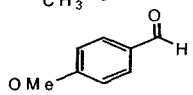
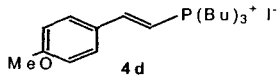
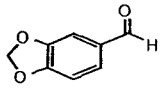
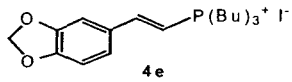
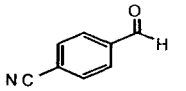
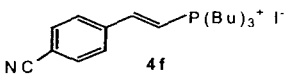
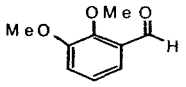
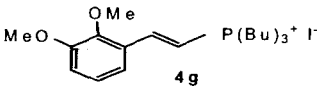
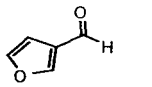
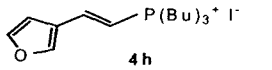
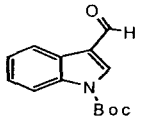
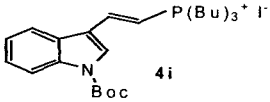
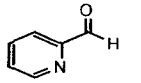
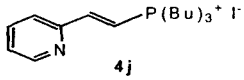
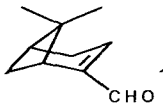
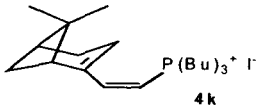
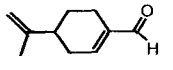
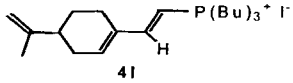
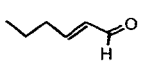
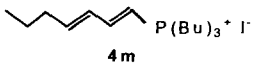
THF, 20 °C, 13h) and that this salt is stable in solid form and in $CDCl_3$ solution for at least 2 months. The stability of the iodide salt is most likely due to the weaker potential for Si-I bond formation. A general procedure was then developed for the selective Peterson reaction through formation of the anion of **3**, generated under kinetically controlled conditions, reacting with a range of aldehydes.

Thus, a THF solution of **3** was cooled to -78 °C and one equivalent of *s*-BuLi added providing a yellow solution of the ylide to which was added one equivalent of 4-chlorobenzaldehyde. The dry-ice bath was removed after 2 h and the reaction allowed warming to room temperature. The desired vinylphosphonium salt **4a** was isolated in 90% yield and with high stereoselectivity favouring the (*E*)-olefin. The reaction proved to be very general for a range of both electron rich and electron deficient aromatic aldehydes, all of which yielded the desired phosphonium salts in excellent yield and high stereoselectivity (Table 1, entries 1 to 7). In addition, heterocyclic derivatives could be prepared from 3-substituted furan, indole and pyridine derivatives in high yields but with lower stereocontrol (Table 1, entries 8 to 10).

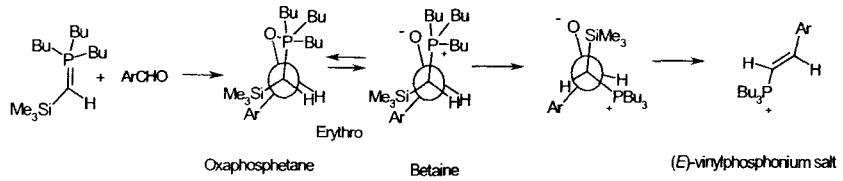
The synthetic utility of this novel reaction as a route to conjugated 1,3-dienylphosphonium salts was also investigated with a range of unsaturated aldehydes (Table 1, entries 11-13). The isolated yields were invariably good in all of the cases investigated; however the reactions proceeded with lower stereoselectivity. The reaction was also investigated with hexanal, which provided a 60 % yield of a 3:1, (*Z*):(*E*) mixture of the corresponding vinyl phosphonium salts. In this case a significant amount (35%) of the tributyl(methyl)phosphonium salt was also formed which we attribute to protonation

and enolate-induced desilylation of the ylide derivative of **3**. High chemoselectivty appears to be restricted to non-enolizable aldehydes at present.

Table 1. Reaction of (TMS)CHPBu$_3$ with aldehydes)

Entry	Aldehyde	Vinylphosphonium salt	(*E*):(*Z*)	Yield (%)
1		 **4a**	49:1	90
2		 **4b**	49:1	95
3		 **4c**	49:1	92
4		 **4d**	49:1	91
5		 **4e**	49:1	85
6		 **4f**	49:1	90
7		 **4g**	49:1	90
8		 **4h**	5:1	85
9		 **4i**	3:1	99
10		 **4j**	3:1	90
11		 **4k**	1:3	78
12		 **4l**	1:3	75
13		 **4m**	1.1:1	77

The high chemoselectivity observed favouring Peterson elimination over Wittig-type elimination and general stereoselectivity favouring (*E*)-vinylphosphonium salts also offers some interesting insights into the mechanism of the Wittig reaction itself. Although the initial formation of oxaphosphetanes is now accepted,[16a] a clear, stepwise account of the reaction mechanism is still debated and much discussion has been made over the relative importance of oxaphosphetane versus betaine intermediates in the Wittig reaction.[16b] In the present case, the observed Peterson elimination is revealing as it requires free-rotation about the central C-C bond of a betaine intermediate, prior to *O*-silyl transfer and elimination. This is strong evidence that the oxaphosphetane readily ionizes to the betaine intermediate, under kinetically controlled conditions, in contrast to a direct elimination of tributylphosphane oxide, which would yield the corresponding vinylsilane. The high (*E*)-stereoselection observed can be rationalized in terms of the currently accepted transition states leading to the oxaphosphetane intermediates.[19a] Relief of torsional and 1,2-non-bonding interactions between the TMS group and aldehyde substituents and of 1,3-steric effects between the alkyl groups on phosphorus and the aryl substituent of the aldehyde are both expected to favour the puckered *cis* transition state, leading to the *erythro* oxaphosphetane, as shown in Scheme 3. Oxaphosphetane opening, bond rotation and Peterson-type elimination then provides the (*E*)-vinylphosphonium salt.



Scheme 3. Stereoselectivty favouring (*E*)-vinylphosphonium salts *via* the kinetic *erythro* betaine.

The overall results appear to indicate that the predominantly (*E*)-vinylphosphonium stereoselectivity is due to kinetic control involving Peterson *syn*-elimination from the *erythro* betaine. The transition state leading to the diastereomeric oxaphosphetane (and hence *threo* betaine) intermediate may be slightly more favourable on the basis of electronic effects. 1,3-Secondary orbital interations between the electron rich π-molecular orbital system in entry 8 or 9, or the lone pair in the case of entry 10, and empty *d*-orbital on phosphorus would be expected to stabilize the planar *trans* transition state, thus explaining the lower stereoselectivities that are observed in those cases.

It is difficult to rationalize the prior report on the synthesis of a vinylsilane from an α–silyl ylide,[13a] although no experimental procedure or spectral data of the product were presented. The reaction of silylated ylides is reported to be complex, however we note that many of the earlier methods [12,13] employ an excess of base or carbonyl component, use less reactive ketones such as benzophenone and often contain excess of coordinating halide, particularly chloride, which is prone to desilylate the necessary intermediates.[12] The clean synthesis of the stable silylphosphonium iodide salt **3**, subsequent generation of its ylide derivative and stoichiometric reaction with aldehydes at low temperature is now shown to be highly selective for the formation of vinylphosphonium salts for the first time.

Conclusion:

We have shown that α-trimethylsilyl (methyl)phosphonium iodide may be prepared from the reaction of tributylphosphine and iodomethyltrimethylsilane and that its ylide derivative adds cleanly to aromatic and unsaturated aldehydes, eliminating selectively in

Peterson fashion to yield vinylphosphonium salts in excellent yield and high (*E*)-stereoselectivity.

References:

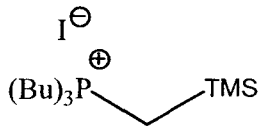
1. Hofmann, A. W. *Annalen der Chemie. Suppl.* 1, **1861**, 275-312.
2. Seyferth, D.; Fogel, J. S.; Heeren, J. K. *J. Am. Chem. Soc.* **1964**, 86, 307-308.
3. (a) Keough, P. T.; Grayson, M. *J. Org. Chem.* **1964**, 29, 631-635. (b) Bonjouklian, R.; Ruden, R. A. *J. Org. Chem.* **1977**, 42, 4095-4098. (c) Posner, G. H.; Lu, S. B. *J. Am. Chem. Soc.* **1985**, 107, 1424-1426.
4. (a) Schweizer, E. E.; Bach, R. D. *J. Org. Chem.* **1964**, 29, 1746. (b) Schweizer, E. E. *J. Am. Chem. Soc.* **1964**, 86, 2744. (c) Schweizer, E.E.; Light, K. K. *J. Am. Chem. Soc.* **1964**, 86, 2963. (d) Schweizer, E. E.; O'Neill, G. J. *J. Org. Chem.* **1965**, 30, 2082-2083. (e) Schweizer, E. E.; Smucker, L. D.; Votral, R. J. *J. Org. Chem.* **1966**, 31, 467-471.
5. For a selection of examples see: (a) Meyers, A. I.; Lawson, J. P.; Carver, D. R. *J. Org. Chem.* **1981**, 46, 3119-3123. (b) Just, G.; O'Connor, B. *Tetrahedron Lett.* **1985**, 26, 1799-1802. (c) Karatholuvhu, M. S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2004**, 126, 14314-14315. (d) Oelke, A. J.; Kumarn, S.; Longbottom, D. A.; Ley, S. V. *Synlett* **2006**, 2548-2552. (e) Kumaran, S.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2006**, 3211-3213.
6. Monkowius, U. V.; Nogai, S. D.; Schmidbaur, H. *J. Am. Chem. Soc.* **2004**, 126, 1632-1633.
7. (a) Huang, C. C.; Duan, J. P.; Wu, M. Y.; Liao, F. L.; Wang, S. L.; Cheng, C. H. *Organometallics* **1998**, 17, 676-682. (b) Kowalski, M. H.; Hinkle, R. J.; Stang, P.

J. *J. Org. Chem.* **1989**, 54, 2783-2784. (c) Hinkle, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, 55, 5033-5036.

8. Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2000**, 122, 2287-2388.
9. Ohmori, H.; Tanakanmi, T.; Masui, M. *Chem. Pharm. Bull.* **1987**, 35, 4960-4963.
10. McNulty, J.; Das, P. *Chem. Commun.* **2008**, 1244-1245.
11. McNulty, J.; Das, P. Gosciniak, D. *Tetrahedron Lett.* **2008**, 49, 281-285.
12. (a) Gilman, H.; Tomasi, R. A. *J. Org. Chem.* **1962**, 27, 3647-3650. (b) Miller, N. E. *J. Am. Chem. Soc.* **1965**, 87, 390-391. (c) Schmidbaur, H.; Malisch, W. *Chem. Ber.* **1970**, 103, 3448-3458. (d) Seyferth, D.; Singh, G. *J. Am. Chem. Soc.* **1965**, 87, 4156-4162.
13. (a) Schmidbaur, H.; Tronich, W. *Chem. Ber.* **1967**, 100, 1032-1050. (b) Schmidbaur, H.; Stuhler, H. *Angew. Chem. Int. Ed.* **1973**, 12, 321-322. (c) Bestmann, H. J. *Pure & Appl. Chem.* **1980**, 52, 771-788.
14. This reagent is available from the Aldrich Chemical Company.
15. The reaction of triphenylphosphine with chloromethyltrimethylsilane proceeds slowly in THF at room temperature (5% conversion after 24 h) and 50% conversion after overnight reflux yielding a mixture of α-trimethylsilyl(methyl) triphenylphosphonium and triphenylmethyl-phosphonium salts.
16. (a) Robiette, R.; J. Richardson, J.; Aggarwal, V. K.; Harvery, J. N. *J. Am. Chem. Soc.* **2006**, 28, 2394-2409. (b) Edmonds, M.; Abell, A. in *Modern Carbonyl Olefination, Methods and Applications*, (Ed. T. Takeda), Wiley-VCH, Weinheim, **2004**, pp.1-17.

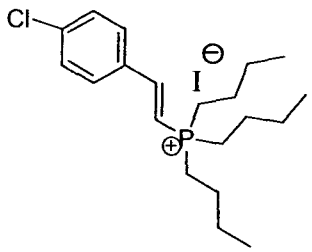
Experimental:

Trimethylsilyl-methyl-tributylphosphonium iodide (3):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed (iodomethyl)trimethylsilane (200 μL, 1.346 mmol) under argon and dry THF (2.7 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at room temperature whereupon tributylphosphine (353 μL, 1.413 mmol) was added slowly to the reaction flask. The flask was maintained at room temperature for 13 h. Solvent was removed under vacuum to yield the title compound, 555 mg, (99%) as a white crystalline solid. Mp 101-102 °C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.30 (s, 9H), 0.95 (m, 9H), 1.53 (m, 12H), 1.87 (d, J_{PH} = 17.0 Hz, 2H), 2.36 (m, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 1.0, 6.9 (d, J_{PC} = 42.3 Hz), 13.6, 22.2 (d, J_{PC} = 49.2 Hz), 23.9 (d, J_{PC} =12.1 Hz), 24.1; ^{31}P NMR (80 MHz, $CDCl_3$): δ 34.9; HRMS $(M)^{+}$ calcd. for $C_{16}H_{38}PSi$: 289.2468, found: 289.2480.

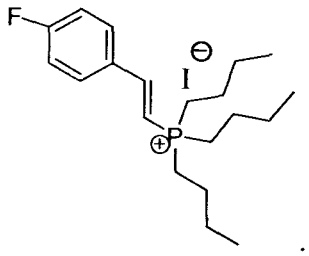
***(E)*-4-Chloro-styryltributylphosphonium iodide (4a):**



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL)

was added to make a 0.5 M solution. The flask was stirred for 15 min. at -78 °C whereupon *s*-BuLi (360μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of 4-chlorobenzaldehyde (71 mg, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 211.8mg, (90%) as yellowish viscous solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.94 (m, 9H), 1.53 (m, 12H), 2.55 (m, 6H), 7.08 (dd, J_{HH} = 17.2 Hz, J_{PH} = 17.2 Hz, 1H), 7.34 (d, J_{HH} = 8.3 Hz, 2H), 7.75 (m, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.6, 20.2 (d, J_{PC} = 50.3 Hz), 23.7, 23.9 (d, J_{PC} = 18.3 Hz), 105.4 (d, J_{PC} = 80.5 Hz), 129.3, 130.2, 132.4 (d, J_{PC} = 18.1 Hz), 137.6, 151.7 (d, J_{PC} = 3.8 Hz); ^{31}P NMR (80 MHz, $CDCl_3$): δ 27.9; HRES MS $(M)^+$ calcd. for $C_{20}H_{33}PCl$: 339.1997, found: 339.2008.

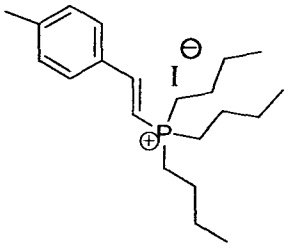
(*E*)-4-Fluoro-styryltributylphosphonium iodide (4b):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C

whereupon *s*-BuLi (360 μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of 4-fluorobenzaldehyde (53.3 μL, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 216 mg, (95%) as yellowish viscous solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.94 (m, 9H), 1.52 (m, 12H), 2.55 (m, 6H), 7.05 (m, 3H), 7.56 (m, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.6, 20.2 (d, J_{PC} = 50.3 Hz), 23.7, 23.9 (d, J_{PC} = 18.0 Hz), 104.3 (d, J_{PC} = 80.3 Hz), 116.2, 128.5 (d, J_{PC} = 18.1 Hz), 131.2, 151.7, 167.2; ^{31}P NMR (80 MHz, $CDCl_3$): δ 27.8; HRES MS $(M)^+$ calcd. for $C_{20}H_{33}PF$: 323.2299, found: 323.2304.

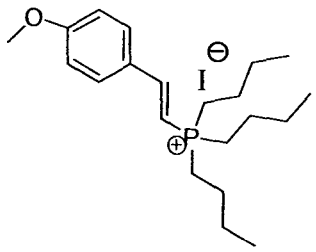
(*E*)-4-Methyl-styryltributylphosphonium iodide (4c):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (360 μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40

min, a 0.5 M solution (in THF) of 4-methylbenzaldehyde (60.1 μL, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 207.3 mg, (92%) as yellowish viscous solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.95 (m, 9H), 1.52 (m, 12H), 2.35 (s, 3H), 2.55 (m, 6H), 6.86 (dd, J_{HH} = 17.8 Hz, J_{PH} = 17.8 Hz, 1H), 7.19 (d, J_{HH} = 8.1 Hz, 2H), 7.62 (m, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.5, 20.1 (d, J_{PC} = 48.8 Hz), 21.5, 23.5, 23.7 (d, J_{PC} = 18.1 Hz), 103.0 (d, J_{PC} = 79.1 Hz), 128.7, 129.6, 131.2 (d, J_{PC} = 16.7 Hz), 142.0, 152.8 (d, J_{PC} = 2.3 Hz); ^{31}P NMR (80 MHz, $CDCl_3$): δ 27.6; HRES MS $(M)^+$ calcd. for $C_{21}H_{36}P$: 319.2570, found: 319.2555.

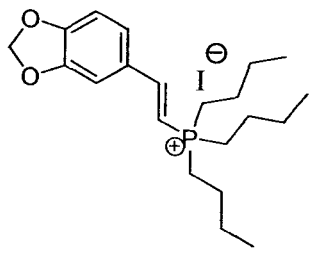
(*E*)-4-Methoxy-styryltributylphosphonium iodide (4d):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (360 μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40

min, a 0.5 M solution (in THF) of 4-methoxybenzaldehyde (61.5 μL, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 212.4 mg, (91%) as yellowish viscous solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.92 (m, 9H), 1.51 (m, 12H), 2.53 (m, 6H), 3.78 (s, 3H), 6.75 (dd, J_{HH} = 17.8 Hz, J_{PH} = 17.8 Hz, 1H), 6.86 (d, J_{HH} = 7.5 Hz, 2H), 7.60 (dd, J_{HH} = 17.8 Hz, J_{PH} = 19.3 Hz, 1H), 7.72 (d, J_{PH} = 7.5 Hz, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.6, 20.3 (d, J_{PC} = 49.7 Hz), 23.6, 23.8 (d, J_{PC} = 17.1 Hz), 55.1, 100.6 (d, J_{PC} = 83.4 Hz), 114.4, 126.7 (d, J_{PC} = 18.3 Hz), 130.7, 152.4, 162.4; ^{31}P NMR (80 MHz, $CDCl_3$): δ 27.5; HRES MS $(M)^+$ calcd. for $C_{21}H_{36}OP$: 335.2512, found: 335.2504.

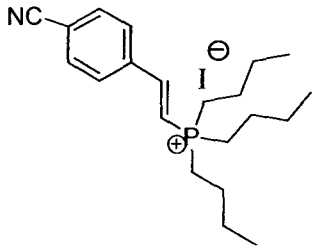
(*E*)-4-(3',4'-Methylenedioxy)styryltributylphosphonium iodide (4e):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (360 μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40

min, a 0.5 M solution (in THF) of piperonal (75.8 mg, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 195 mg, (85%) as yellowish viscous solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.92 (m, 9H), 1.50 (m, 12H), 2.55 (m, 6H), 5.90 (s, 2H), 6.71 (dd, J_{HH} = 17.5 Hz, J_{PH} =17.5 Hz, 1H), 6.84 (d, J_{HH} = 8.5 Hz, 2H), 7.22 (s, 1H), 7.59 (dd, J_{HH} = 17.5 Hz, J_{PH} = 20.9 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.6, 20.1 (d, J_{PC} = 47.2 Hz), 23.8, 23.9 (d, J_{PC} = 19.3 Hz), 101.7 (d, J_{PC} = 64.8 Hz), 102.0, 107.0, 108.6, 125.8, 128.6 (d, J_{PC} = 18.8 Hz), 148.6, 150.8, 152.5 (d, J_{PC} = 3.0 Hz); ^{31}P NMR (80 MHz, $CDCl_3$): δ 27.7; HRES MS $(M)^+$ calcd. for $C_{21}H_{34}O_2P$: 349.2282, found: 349.2296.

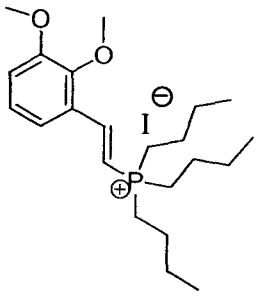
(*E*)-4-Cyano-styryltributylphosphonium iodide (4f):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (360 μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40

min, a 0.5 M solution (in THF) of 4-cyanobenzaldehyde (66.2 mg, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 208 mg, (90%) as yellowish viscous solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.94 (m, 9H), 1.54 (m, 12H), 2.60 (m, 6H), 7.50 (dd, J_{HH} = 17.4 Hz, J_{PH} = 17.4 Hz, 1H), 7.65 (d, J_{HH} = 8.4 Hz, 2H), 8.0 (m, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.6, 20.5 (d, J_{PC} = 49.3 Hz), 23.8, 23.9 (d, J_{PC} = 18.1 Hz), 110 (d, J_{PC} = 81.1 Hz), 114.1, 118.3, 132.6, 135.6, 138.0 (d, J_{PC} =19.7 Hz), 150.8; ^{31}P NMR (80 MHz, $CDCl_3$): δ 28.4; HRES MS $(M)^+$ calcd. for $C_{21}H_{33}NP$: 330.2344, found: 330.2351.

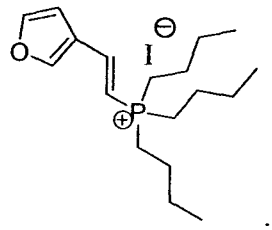
(*E*) -2,3-Dimethoxystyryltributylphosphonium iodide (4g):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (360 μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40

min, a 0.5 M solution (in THF) of 2,3-dimethoxybenzaldehyde (83.9 mg, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 223.7 mg, (90%) as brownish viscous solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.93 (m, 9H), 1.52 (m, 12H), 2.55 (m, 6H), 3.91 (s, 6H), 7.10 (m, 3H), 7.51 (d, J_{HH} = 7.8 Hz, 2H), 7.74 (dd, J_{HH} = 17.9 Hz, J_{PH} = 19.4 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.7, 20.0 (d, J_{PC} = 50.6 Hz), 23.6, 23.7 (d, J_{PC} = 15.2 Hz), 56.2, 61.7, 106.3 (d, J_{PC} = 79.8 Hz), 115.1, 119.7, 124.8, 127.5 (d, J_{PC} = 18.4 Hz), 146.4, 148.0, 152.8; ^{31}P NMR (80 MHz, $CDCl_3$): δ 27.8; HRES MS $(M)^+$ calcd. for $C_{22}H_{38}O_2P$: 365.2599, found: 365.2609.

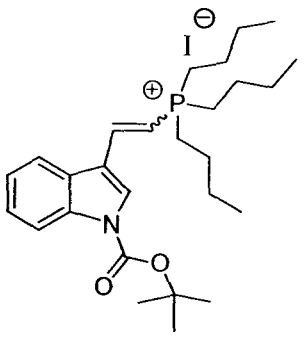
(*E*)-3-furyl-vinyl-tributylphosphonium iodide (4h):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (360 μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40

min, a 0.5 M solution (in THF) of 3-furaldehyde (43.7 μL, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 181.2 mg, (85%) as brownish viscous solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.92 (m, 9H), 1.52 (m, 12H), 2.55 (m, 6H), 6.20 (dd, J_{HH} = 17.9 Hz, J_{PH} = 17.9 Hz, 1H), 6.46 (s, 1H), 6.99 (s, 1H), 7.50 (s, 1H), 7.76 (dd, J_{HH} = 17.9 Hz, J_{PH} = 17.9 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.5, 20.3 (d, J_{PC} = 47.5 Hz), 23.6, 23.8 (d, J_{PC} = 18.2 Hz), 99.2 (d, J_{PC} = 79.2 Hz), 112.8, 118.0, 139.8, 146.0, 150.1 (d, J_{PC} = 7.1 Hz); ^{31}P NMR (80 MHz, $CDCl_3$): δ 27.7; HRES MS $(M)^+$ calcd. for $C_{18}H_{32}OP^-$: 295.2199, found: 295.2191.

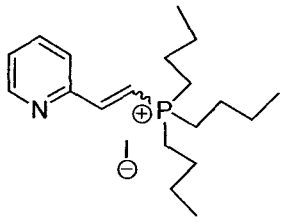
3-(2'-(tributylphosphonium)vinyl)-N-(Boc)-indole iodide (4i):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL)

was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (360 μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of N-(*t*-butoxycarbonyl)indole-3-carboxaldehyde (123.8 mg, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 285.6 mg, (99%) as brownish viscous solid. ***E*** isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.91 (m, 9H), 1.52 (m, 12H), 1.63 (s, 9H), 2.58 (m, 6H), 6.71 (dd, J_{HH} = 18.1 Hz, J_{PH} = 18.1 Hz, 1H), 7.33 (m, 2H), 7.9 (dd, J_{HH} = 18.1 Hz, J_{PH} = 20.6 Hz, 1H), 8.10 (m, 1H), 8.15 (m, 1H), 8.24 (s, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.6, 20.4 (d, J_{PH} = 50.2 Hz), 23.8, 23.9 (d, J_{PH} = 15.0 Hz), 28.2, 82.3, 101.5 (d, J_{PH} = 83.4 Hz), 115.6, 117.0 (d, J_{PH} = 20.5 Hz), 120.8, 124.2, 125.6, 127.0, 131.5, 136.2, 145.5, 148.9; ^{31}P NMR (80 MHz, $CDCl_3$): δ 27.9; HRES MS $(M)^+$ calcd. for $C_{27}H_{43}NO_2P$: 444.3015, found: 444.3031. ***Z*** isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.91 (m, 9H), 1.52 (m, 12H), 1.63 (s, 9H), 2.42 (m, 6H), 5.99 (dd, J_{HH} = 17.6 Hz, J_{PH} = 19.5 Hz, 1H), 7.14 (m, 2H), 7.64 (m, 1H), 7.75 (dd, J_{HH} = 17.6 Hz, J_{PH} = 20.6 Hz, 1H), 7.84 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.6, 20.8 (d, J_{PC} = 51.4 Hz), 23.8, 23.9 (d, J_{PC} = 15.0 Hz), 28.2, 82.3, 92.2 (d, J_{PC} = 88.0 Hz), 112.9 (d, J_{PC} = 19.9 Hz), 113.3, 119.6, 121.8, 123.2, 124.8, 132.8, 137.5, 147.5, 148.9; ^{31}P NMR (80 MHz, $CDCl_3$): δ 26.6; HRES MS $(M)^+$ calcd. for $C_{27}H_{43}NO_2P$: 444.3015, found: 444.3031.

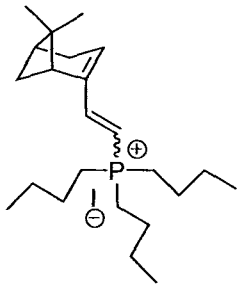
2-(vinyltributylphosphonium)-pyridine iodide (4j):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (360 µL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of 2-pyridinecarboxaldehyde (48.1 µL, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 197 mg, (90%) as yellowish viscous solid. ***E*** isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.92 (m, 9H), 1.53 (m, 12H), 2.60 (m, 6H), 7.19 (dd, J_{HH} = 17.4 Hz, J_{PH} = 19.7 Hz, 1H), 7.30 (dd, J_{HH} = 7.5 Hz, J_{HH} = 4.9 Hz, 1H), 7.74 (dt, J_{HH} = 7.7 Hz, J_{HH} = 1.7 Hz, 1H), 8.0 (d, J_{HH} = 7.7 Hz, 1H), 8.13 (dd, J_{HH} = 17.4 Hz, J_{PH} = 19.3 Hz, 1H), 8.57 (d, J_{HH} = 4.8 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.6, 20.4 (d, J_{PC} = 50.3 Hz), 23.8, 23.9 (d, J_{PC} = 20.0 Hz), 108.3 (d, J_{PC} = 79.8 Hz), 125.6, 126.4, 137.0, 149.9, 151.2 (d, J_{PC} = 7.0 Hz), 153.1; ^{31}P NMR (80 MHz, $CDCl_3$): δ 27.9; HRES MS

$(M)^+$ calcd. for $C_{19}H_{33}NP$: 306.2340, found: 306.2351. ***Z*** isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.81 (m, 9H), 1.37 (m, 12H), 2.53 (m, 6H), 6.20 (dd, J_{HH} = 12.6 Hz, J_{PH} = 19.1 Hz, 1H), 7.43 (dd, J_{HH} = 7.5 Hz, J_{HH} = 4.9 Hz, 1H), 7.62 (d, J_{HH} = 7.7 Hz, 1H), 7.86 (m, 2H), 8.67 (d, J_{HH} = 4.9 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.5, 22.8 (d, J_{PC} = 49.8 Hz), 23.7, 23.9 (d, J_{PC} = 20.1 Hz), 112.2 (d, J_{PC} = 77.5 Hz), 125.9, 127.6, 138.5, 148.8, 150.8, 152.2; ^{31}P NMR (80 MHz, $CDCl_3$): δ 25.1; HRES MS $(M)^+$ calcd. for $C_{19}H_{33}NP$: 306.2340, found: 306.2351.

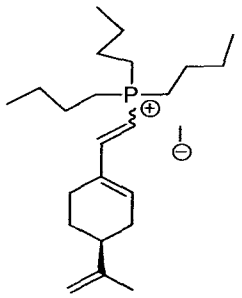
6,6-dimethyl-2-(vinyltributylphosphonium)-bicyclo[3.1.1]hept-2-ene iodide (4k):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (360 μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of (1*R*)-(−)-Myrtenal (78.6 μL, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was

added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 187.6 mg, (78%) as yellowish viscous solid. ***E*** isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.62 (s, 3H), 0.84 (m, 9H), 1.05 (m, 1H), 1.25 (s, 3H), 1.43 (m, 12H), 2.03 (m, 1H), 2.39 (m, 10H), 5.61 (m, 1H), 6.30(s, 1H), 7.24 (dd, J_{HH} = 19.5 Hz, J_{PH} = 19.5 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.2, 20.2 (d, J_{PC} = 50.2 Hz), 20.5, 23.6 (d, J_{PC} = 16.3 Hz), 24.0, 25.6, 30.9, 32.5, 37.7, 40.4, 44.5, 98.7 (d, J_{PC} = 82.3 Hz), 138.4, 145.8 (d, J_{PC} = 7.0 Hz), 153.1; ^{31}P NMR (80 MHz, $CDCl_3$): δ 26.7; HRES MS $(M)^{+}$ calcd. for $C_{23}H_{42}P$: 349.3013, found: 349.3024. ***Z*** isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.71 (s, 3H), 0.84 (m, 9H), 1.07 (m, 1H), 1.23 (s, 3H), 1.43 (m, 12H), 2.06 (m, 1H), 2.39 (m, 10H), 5.67 (m, 1H), 5.88 (s, 1H), 7.05 (dd, J_{HH} = 13.6 Hz, J_{PH} = 42.7 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.2, 22.3 (d, J_{PC} = 49.6 Hz), 20.5, 23.6 (d, J_{PC} = 16.3 Hz), 24.0, 25.8, 30.5, 32.3, 37.8, 39.6, 44.5, 102.4 (d, J_{PC} = 74.8 Hz), 131.9, 144.6, 155.8; ^{31}P NMR (80 MHz, $CDCl_3$): δ 22.0; HRES MS $(M)^{+}$ calcd. for $C_{23}H_{42}P$: 349.3013, found: 349.3024.

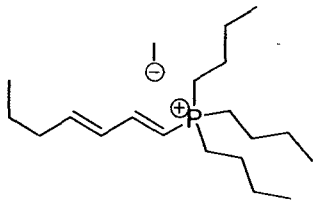
(S)-4-(prop-1-en-2-yl)-1-vinytributylphosphonium-cyclohex-1-ene iodide (4l):



Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C

whereupon *s*-BuLi (360 μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of (1*S*)-(−)-Perillaldehyde (78.6 μL, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 180.4 mg, (75%) as yellowish viscous solid. ***E*** isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.93 (m, 9H), 1.52 (m, 12H), 1.71 (s, 3H), 1.92 (m, 1H), 2.12 (m, 4H), 2.37 (m, 1H), 2.52 (m, 6H), 4.69 (s, 1H), 4.74 (s, 1H), 5.92 (m, 1H), 6.47 (m, 1H), 7.24 (m, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.7, 20.4 (d, J_{PC} = 50.2 Hz), 23.8, 23.9 (d, J_{PC} = 19.0 Hz), 26.8, 29.8, 32.0, 40.5, 100.2 (d, J_{PC} = 82.8 Hz), 109.5, 135.6, 142.5, 148.6, 155.8; ^{31}P NMR (80 MHz, $CDCl_3$): δ 26.1. HRES MS $(M)^+$ calcd. for $C_{23}H_{42}P$: 349.3013, found: 349.3024. ***Z*** isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.93 (m, 9H), 1.52 (m, 12H), 1.73 (s, 3H), 1.92 (m, 1H), 2.12 (m, 4H), 2.37 (m, 1H), 2.52 (m, 6H), 4.70 (s, 1H), 4.77 (s, 1H), 5.79 (m, 1H), 5.92 (m, 1H), 7.24 (m, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.7, 22.3 (d, J_{PC} = 49.7 Hz), 24.0, 24.1 (d, J_{PC} = 19.0 Hz), 26.9, 28.2, 30.9, 40.1, 106.6 (d, J J_{PC} = 74.6 Hz), 109.9, 130.6, 135.6, 148.1, 158.2; ^{31}P NMR (80 MHz, $CDCl_3$): δ 23.7; HRES MS $(M)^+$ calcd. for $C_{23}H_{42}P$: 349.3013, found: 349.3024.

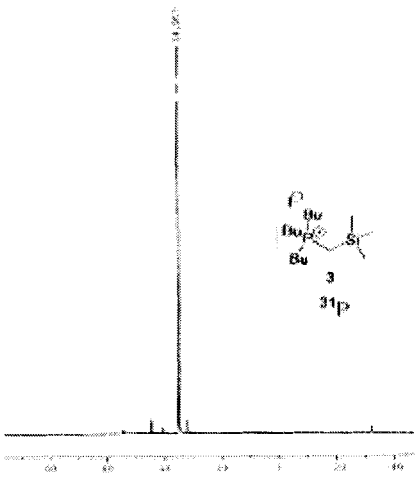
Hexa-1,3-dienyl-tributylphosphonium iodide (4m):

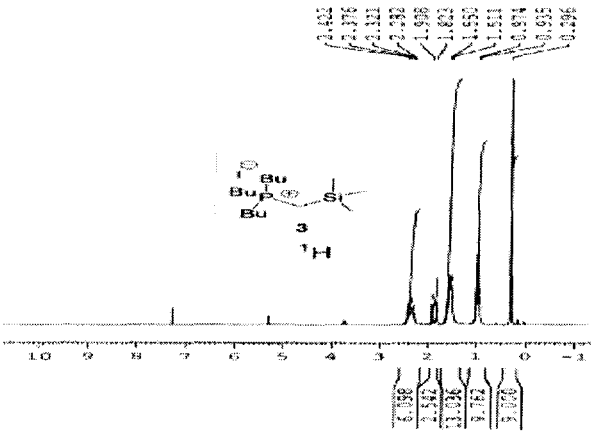


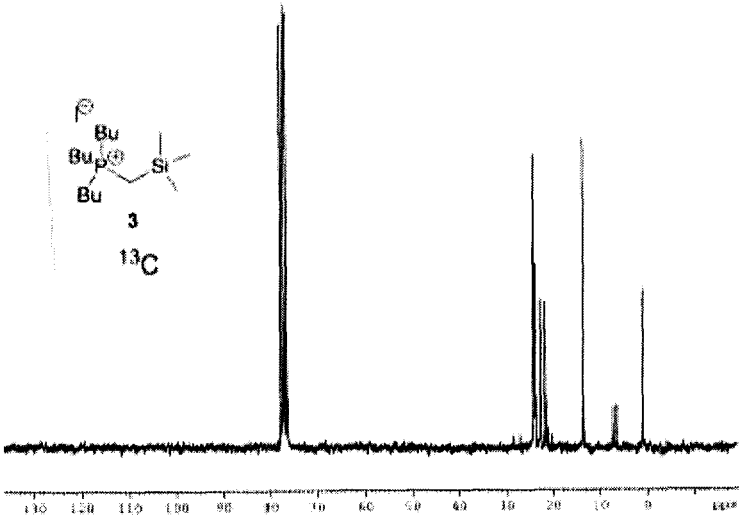
Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl-methyl-tributylphosphonium salt (200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min at -78 °C whereupon *s*-BuLi (360 μL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of 2-hexeneal (58.6 μL, 0.505 mmol) was added slowly to the reaction flask maintained at -78 °C. The flask was kept at -78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask and stirred for 5 min. The slurry was vacuum filtered and dried to yield the title compound, 166.1 mg, (77%) as yellowish viscous solid. ***E*** isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.91 (m, 12H), 1.50 (m, 14H), 2.25 (m, 2H), 2.56 (m, 6H), 6.02 (dd, J_{HH} = 17.5 Hz, J_{HH} = 17.5 Hz, 1H), 6.35 (m, 2H), 7.28 (m, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.5, 20.3 (d, J_{PC} = 50.3 Hz), 23.7, 23.9 (d, J_{PC} = 20.2 Hz), 35.0, 104.4 (d, J_{PC} = 82.0 Hz), 129.3 (d, J_{PC} = 21.0 Hz), 148.3, 153.6; ^{31}P NMR (80 MHz, $CDCl_3$): δ 26.4; HRES MS $(M)^+$ calcd. for $C_{19}H_{38}P$: 297.2707, found: 297.2711. ***Z*** isomer: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.90 (m, 12H), 1.50 (m, 14H), 2.14 (m, 2H), 2.47 (m, 6H), 5.61 (dd, J_{HH} = 14.2 Hz, J_{PH} = 19.1 Hz, 1H), 6.30 (m, 2H), 7.21 (m, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$):

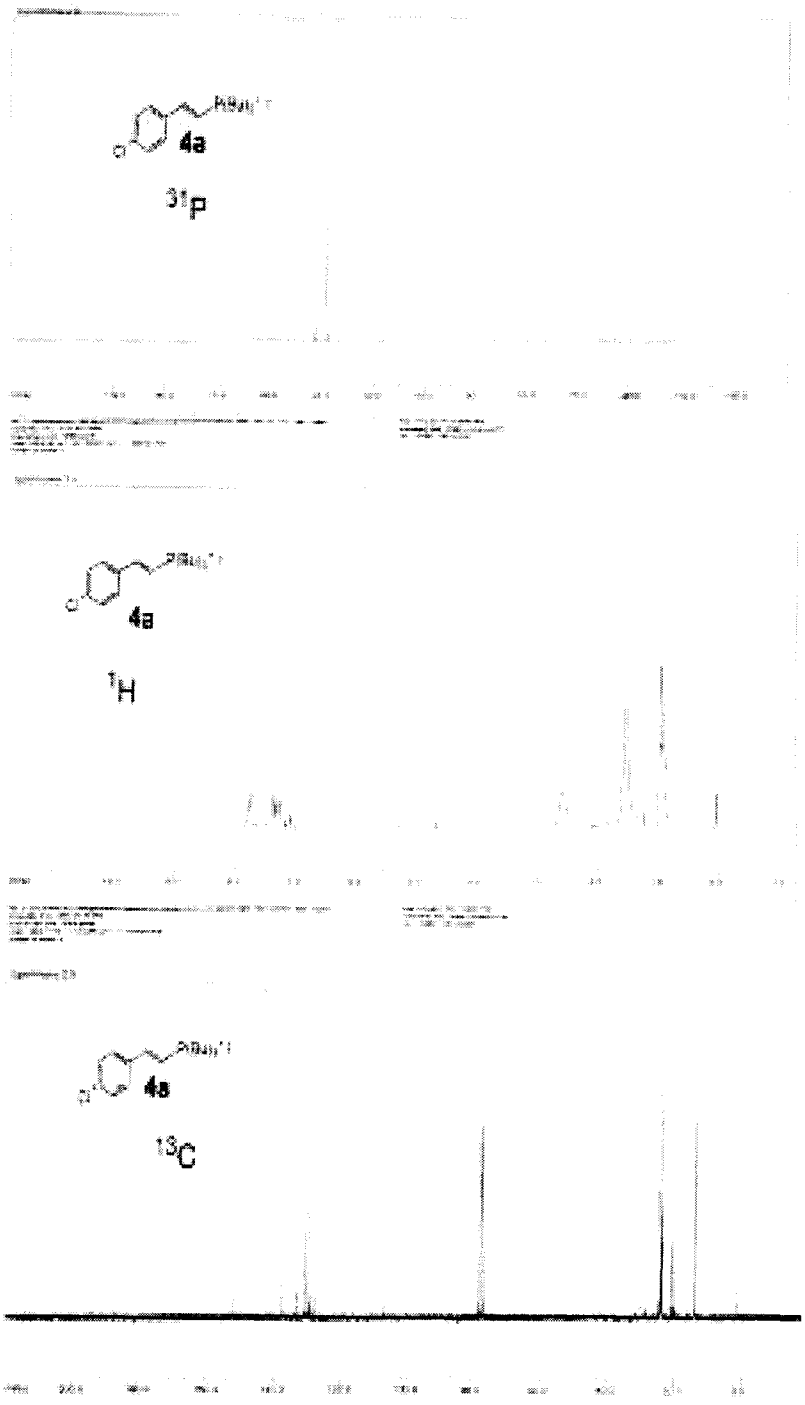
δ 13.6, 21.9 (d, J_{PC} = 49.4 Hz), 23.7, 23.9 (d, J_{PC} = 20.2 Hz), 35.1, 102.1 (d, J_{PC} = 74.6 Hz), 125.2 (d, J_{PC} = 9.1 Hz), 151.6, 154.2; ^{31}P NMR (80 MHz, $CDCl_3$): δ 23.2; HRES MS $(M)^+$ calcd. for $C_{19}H_{38}P$: 297.2707, found: 297.2711.

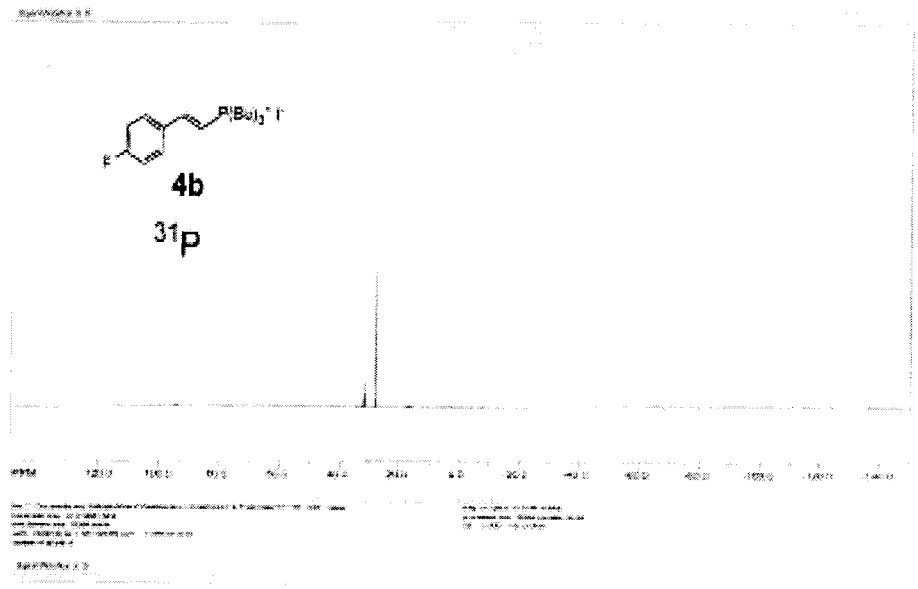
NMR Spectra of New Compounds:

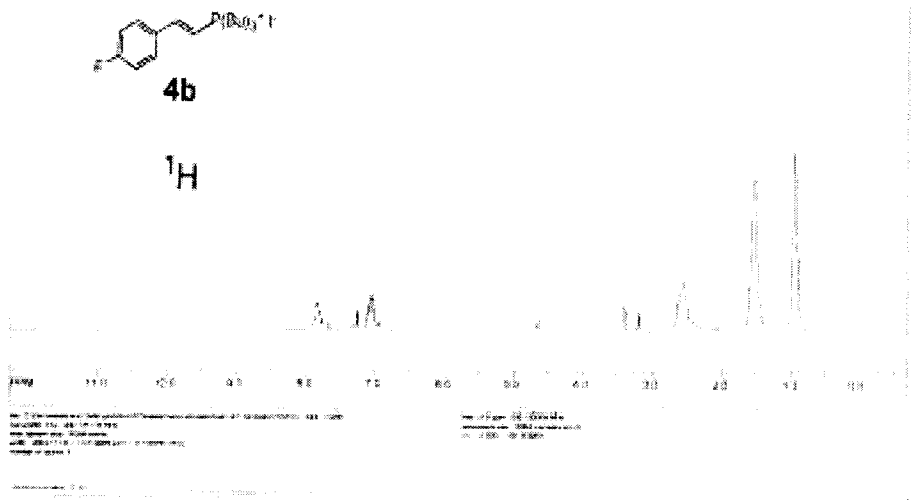


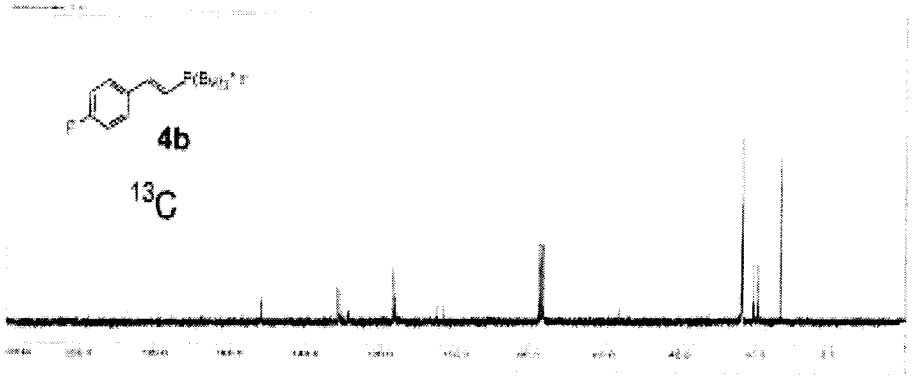


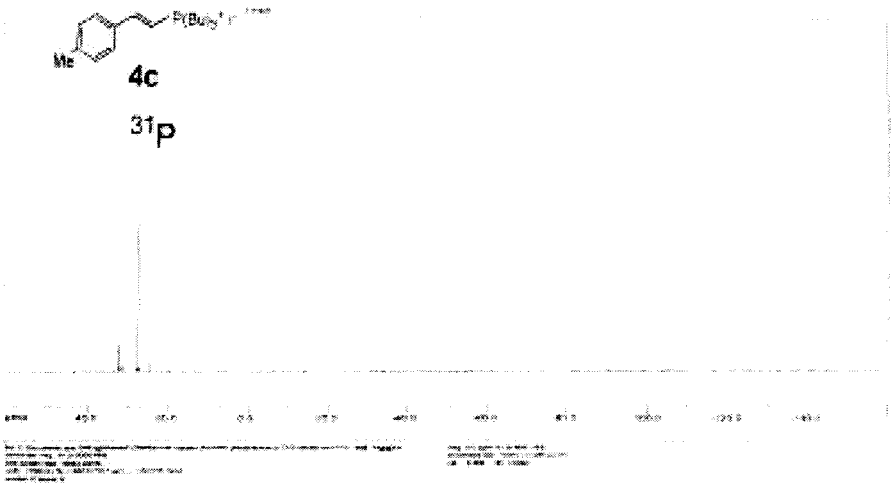


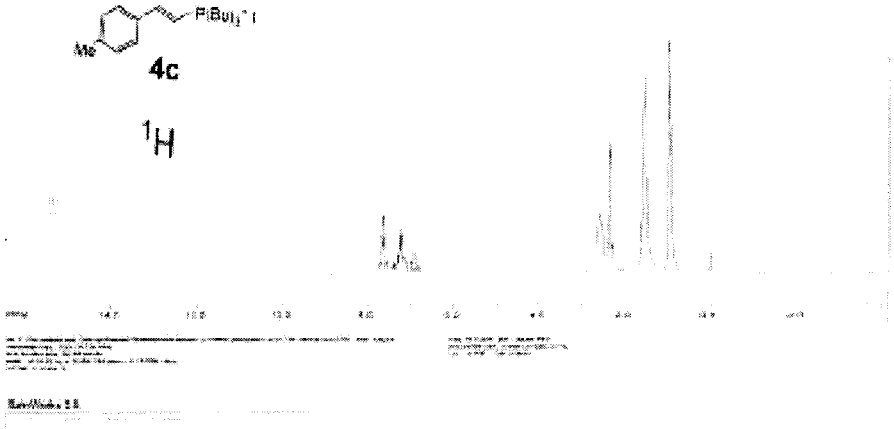

4a
31P
4a
1H
4a
13C

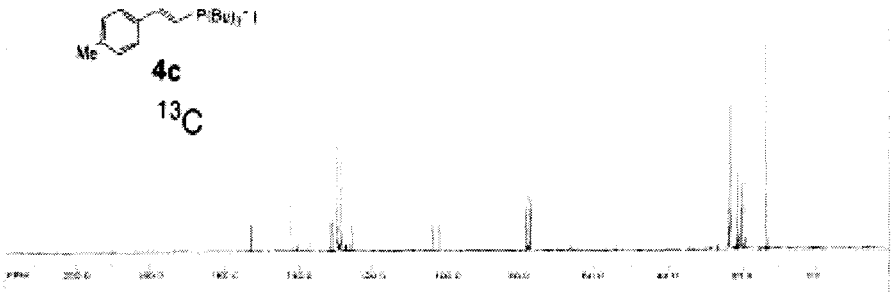

4b
31P

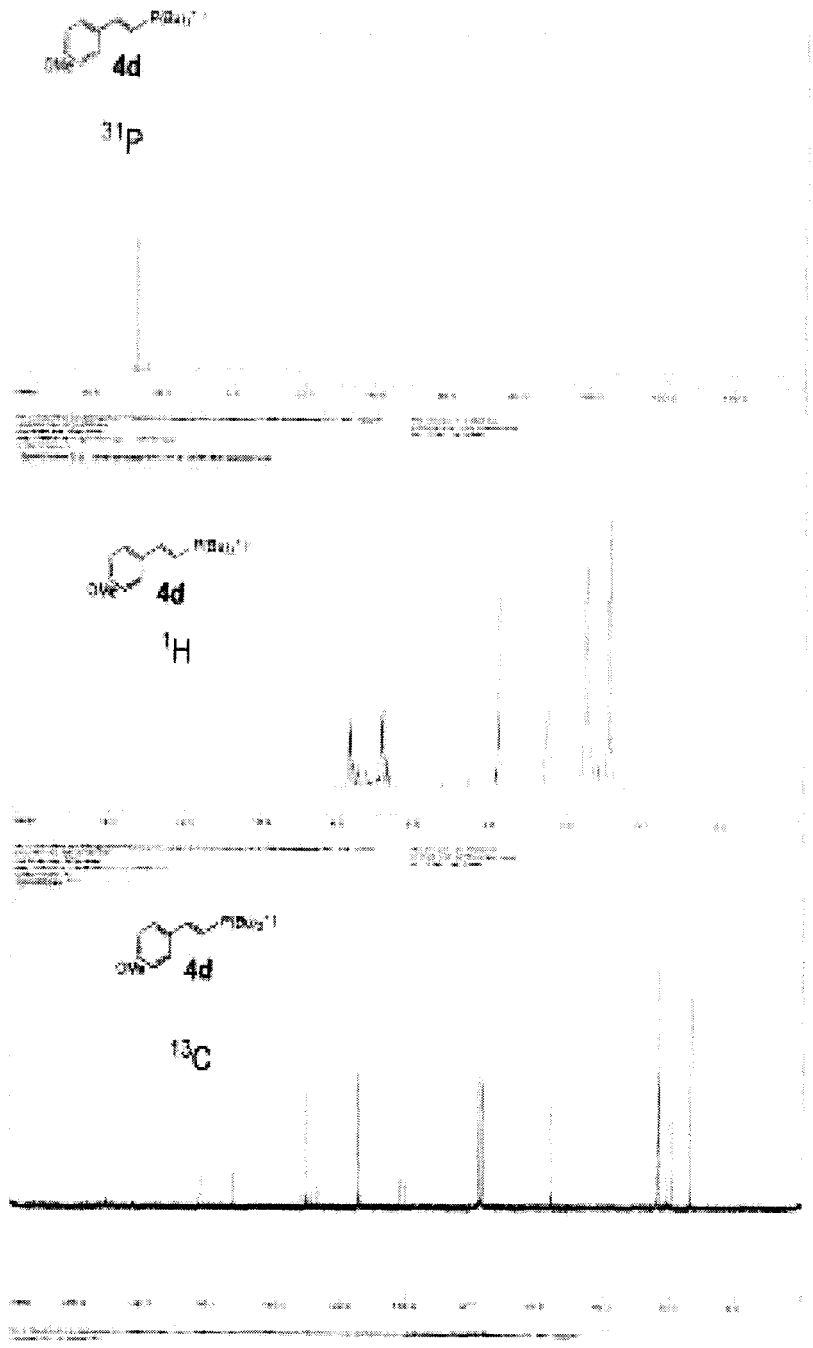

4b
1H

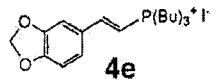

4b
13C


Me
4c
31P


Me
4c
1H

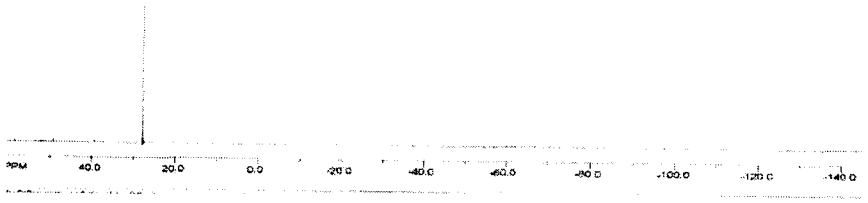

Me
4c
13C

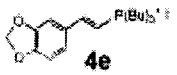

4d
31P
4d
1H
4d
13C



4e

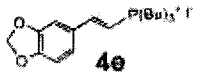
^{31}P





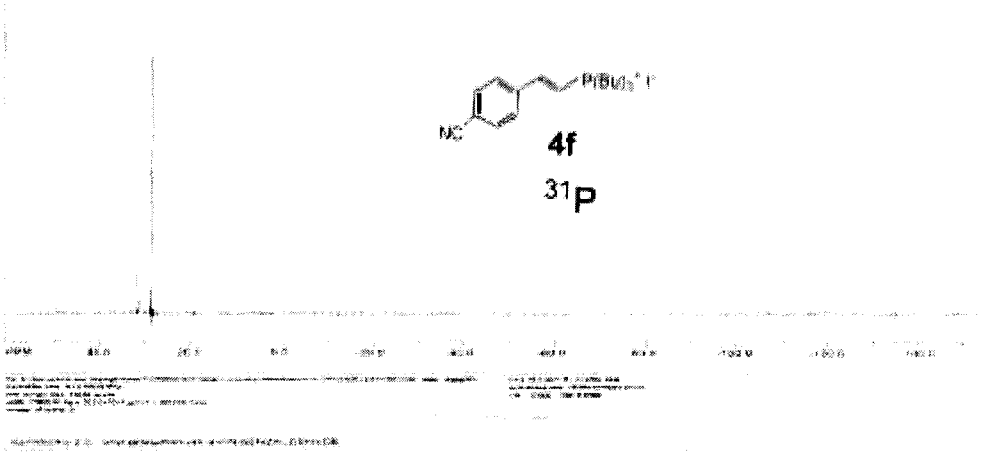
4e

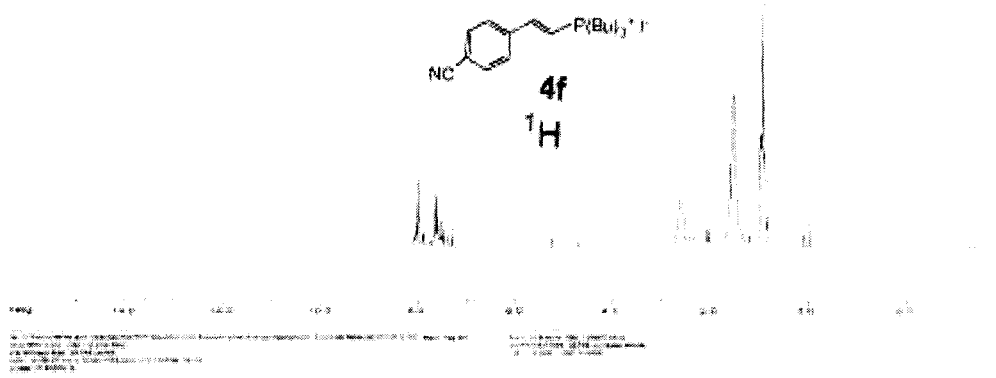
^{1}H

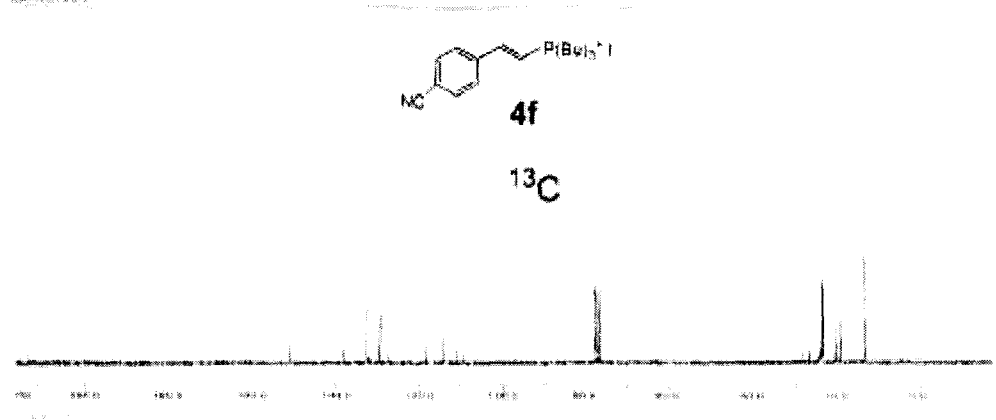


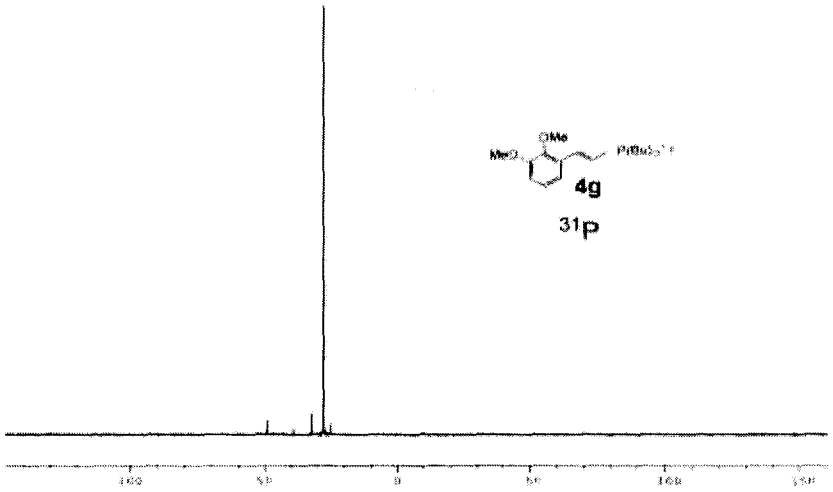
4e

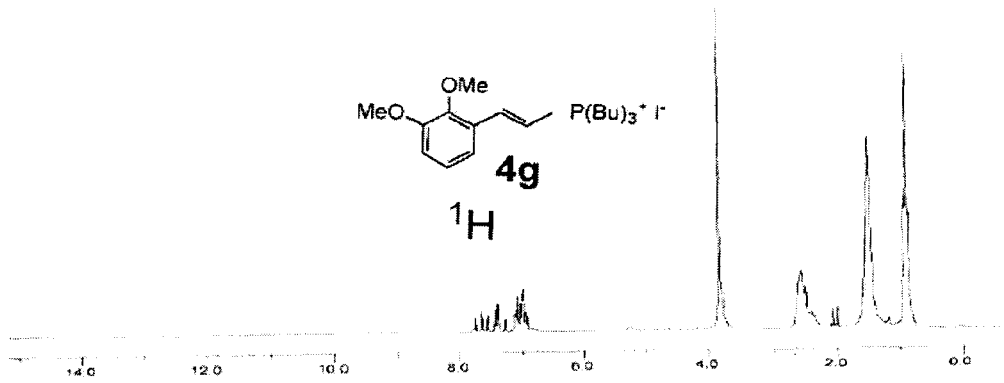
^{13}C

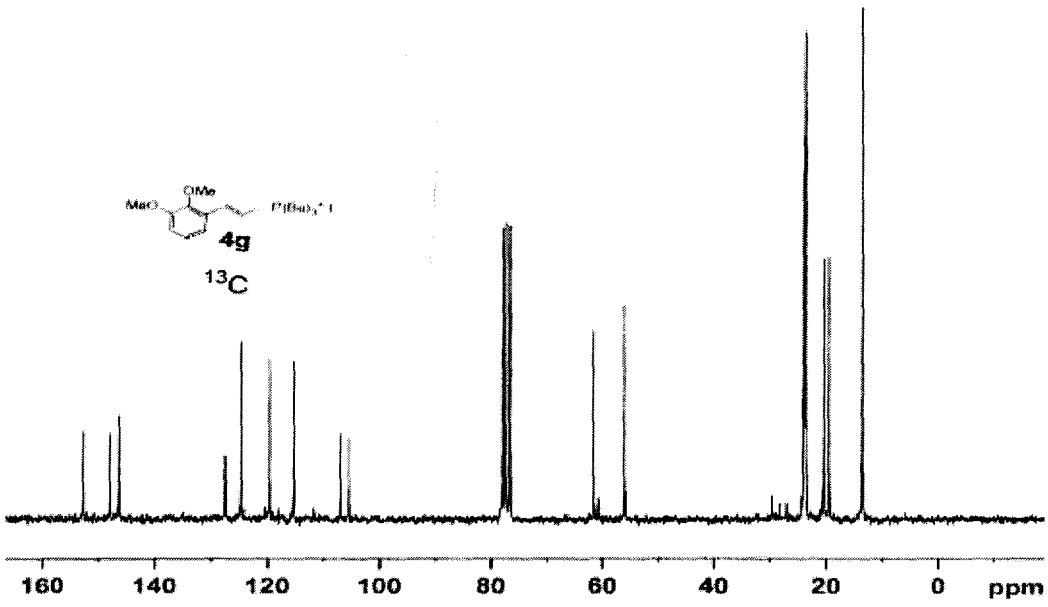

NC
4f
31P

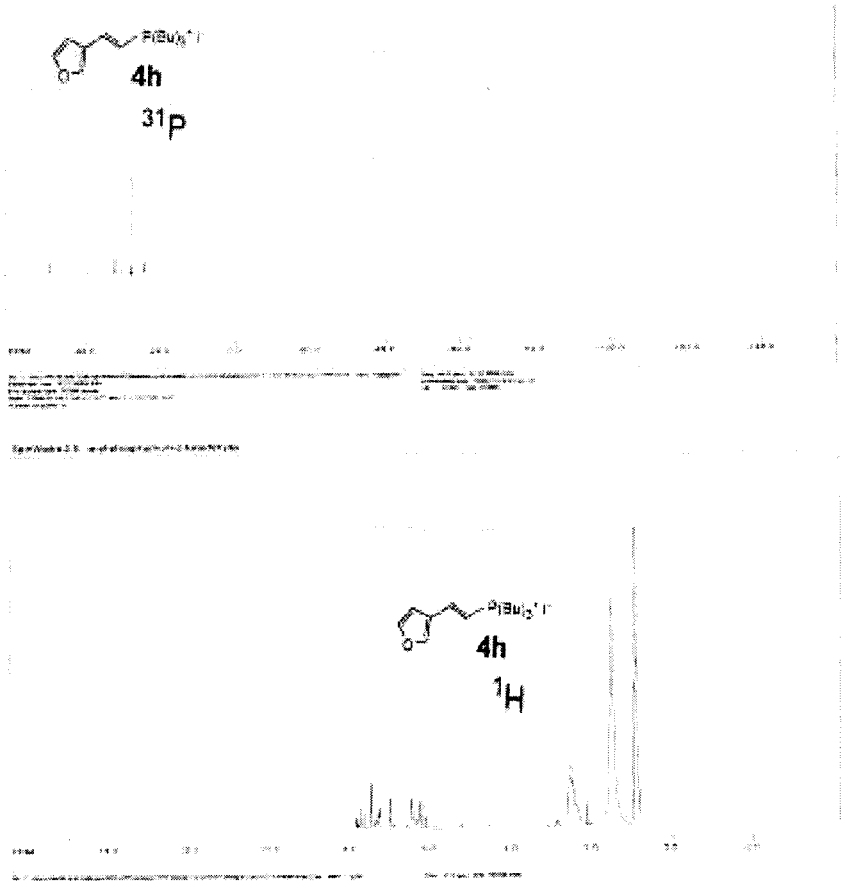

NC
4f
1H

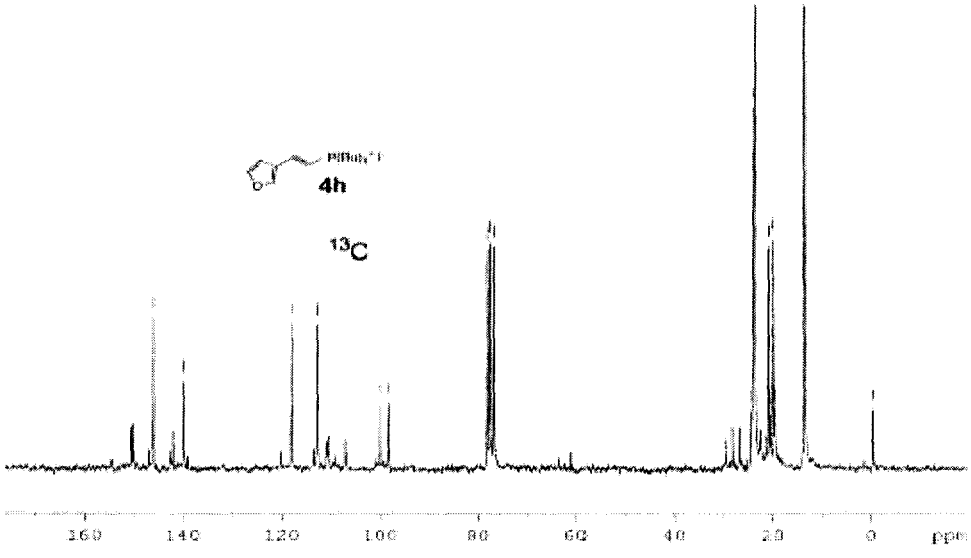

NC
4f
13C

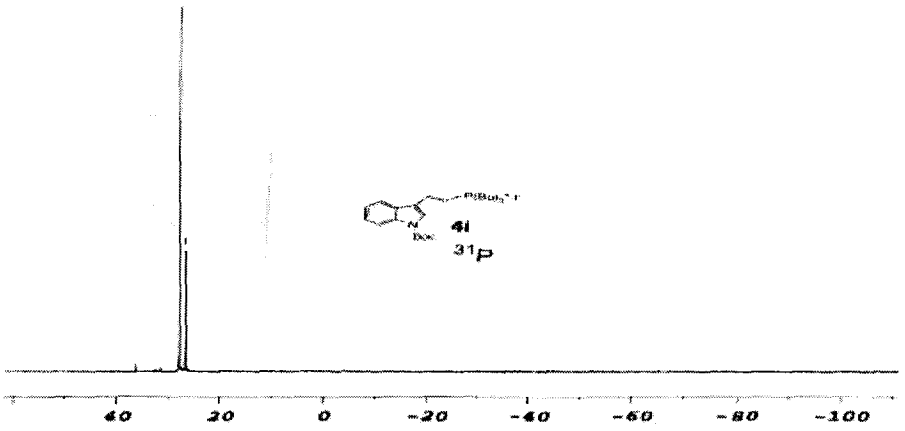

4g
31P

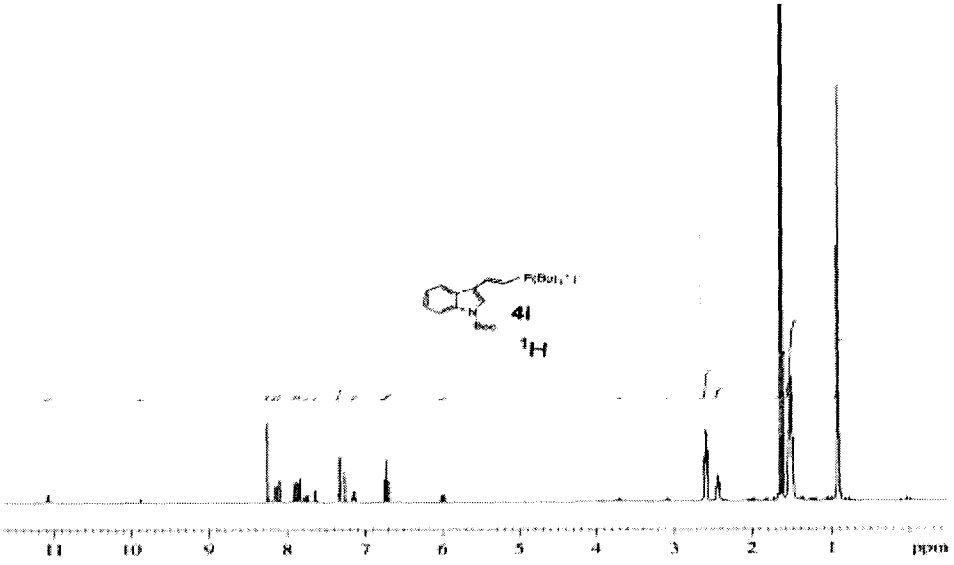

OMe
MeO
P(Bu)3+ I-
4g
1H

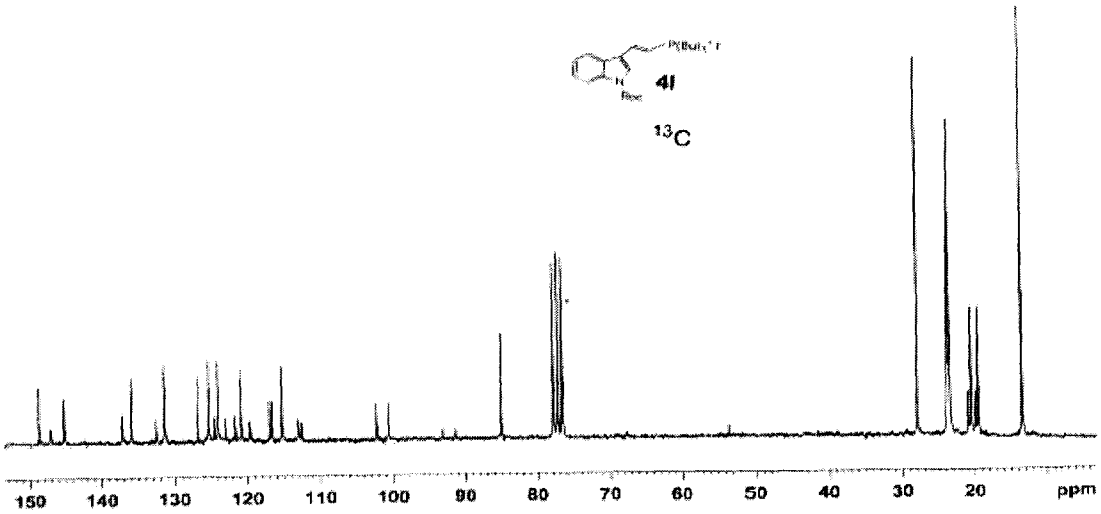

4g
13C
160
140
120
100
80
60
40
20
0
ppm

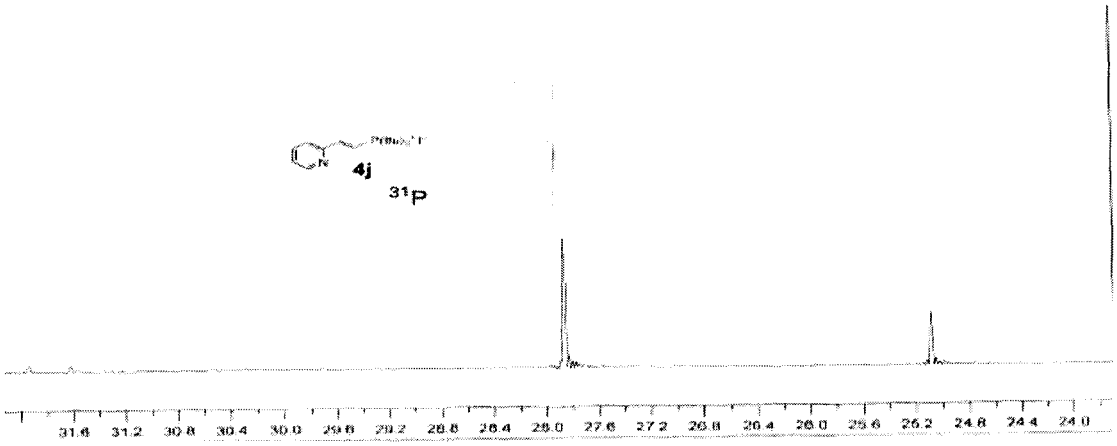

4h
31P
4h
1H

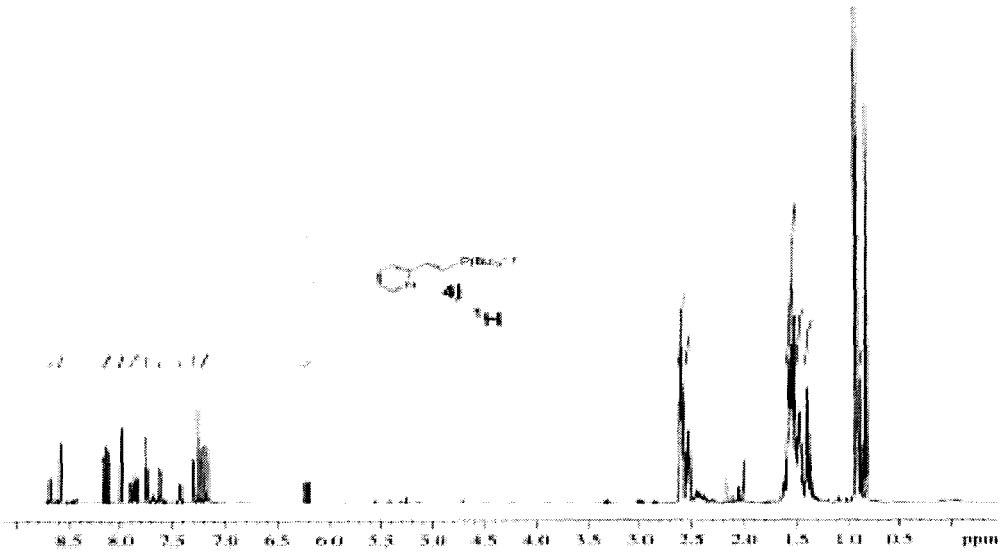

4h
13C
160
140
120
100
80
60
40
20
0
ppm

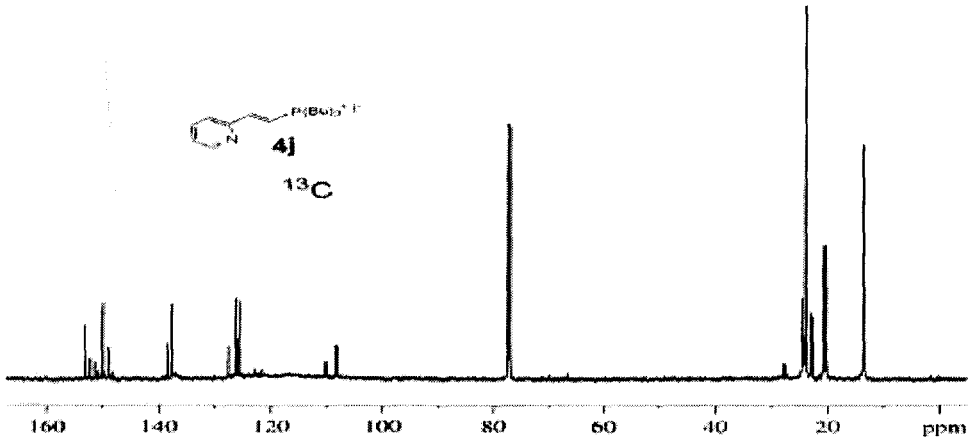

4l
31P
40
20
0
-20
-40
-60
-80
-100

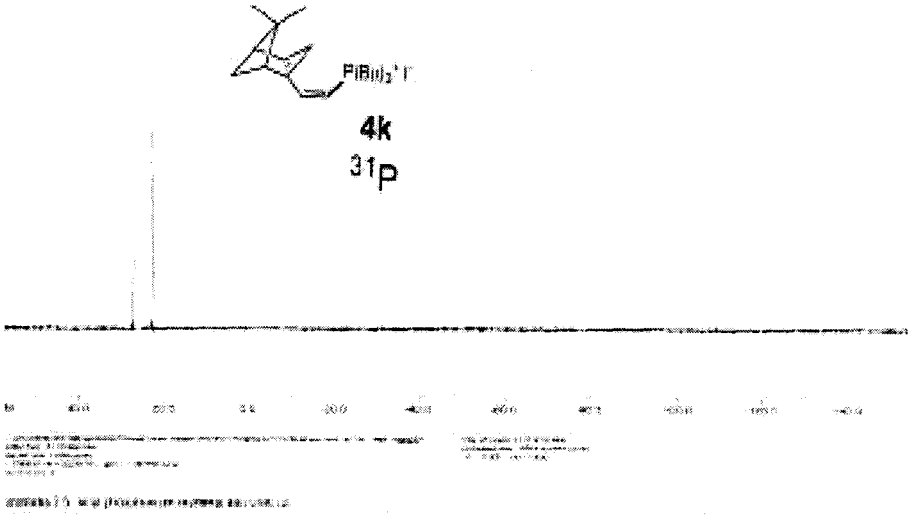

4l
1H
11
10
9
8
7
6
5
4
3
2
1
ppm

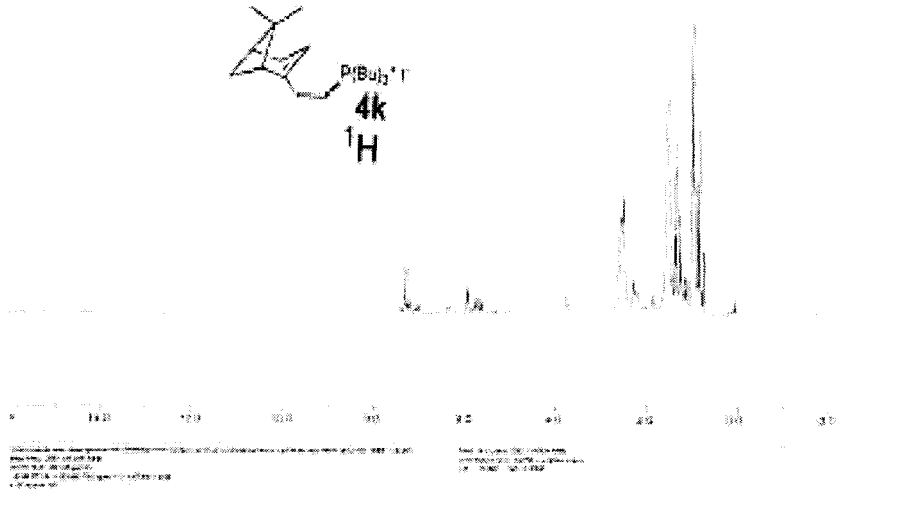

4l
13C
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

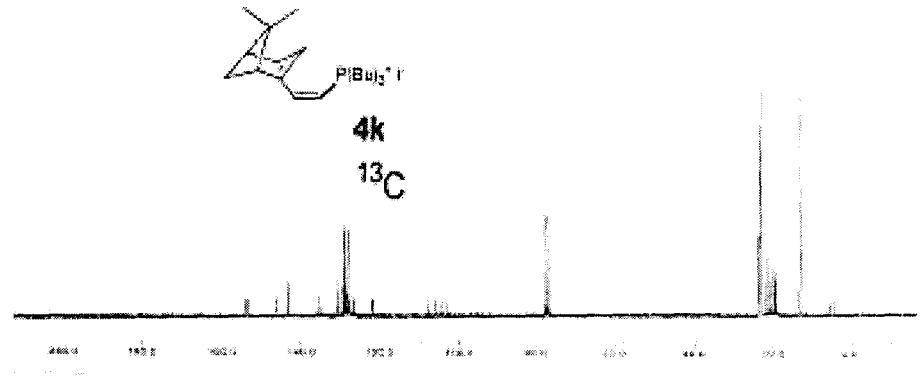

4j
31P

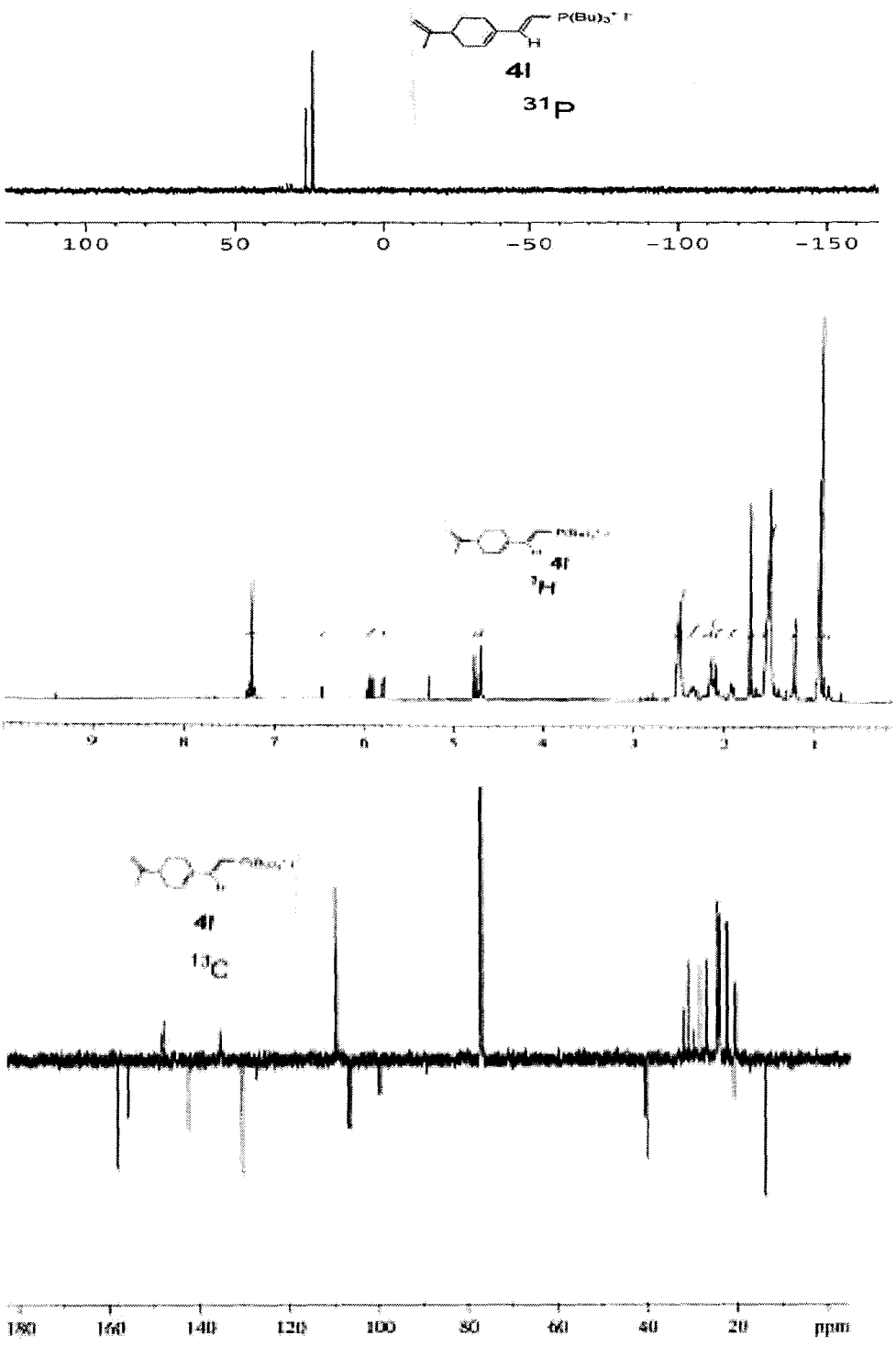

4j
1H
ppm

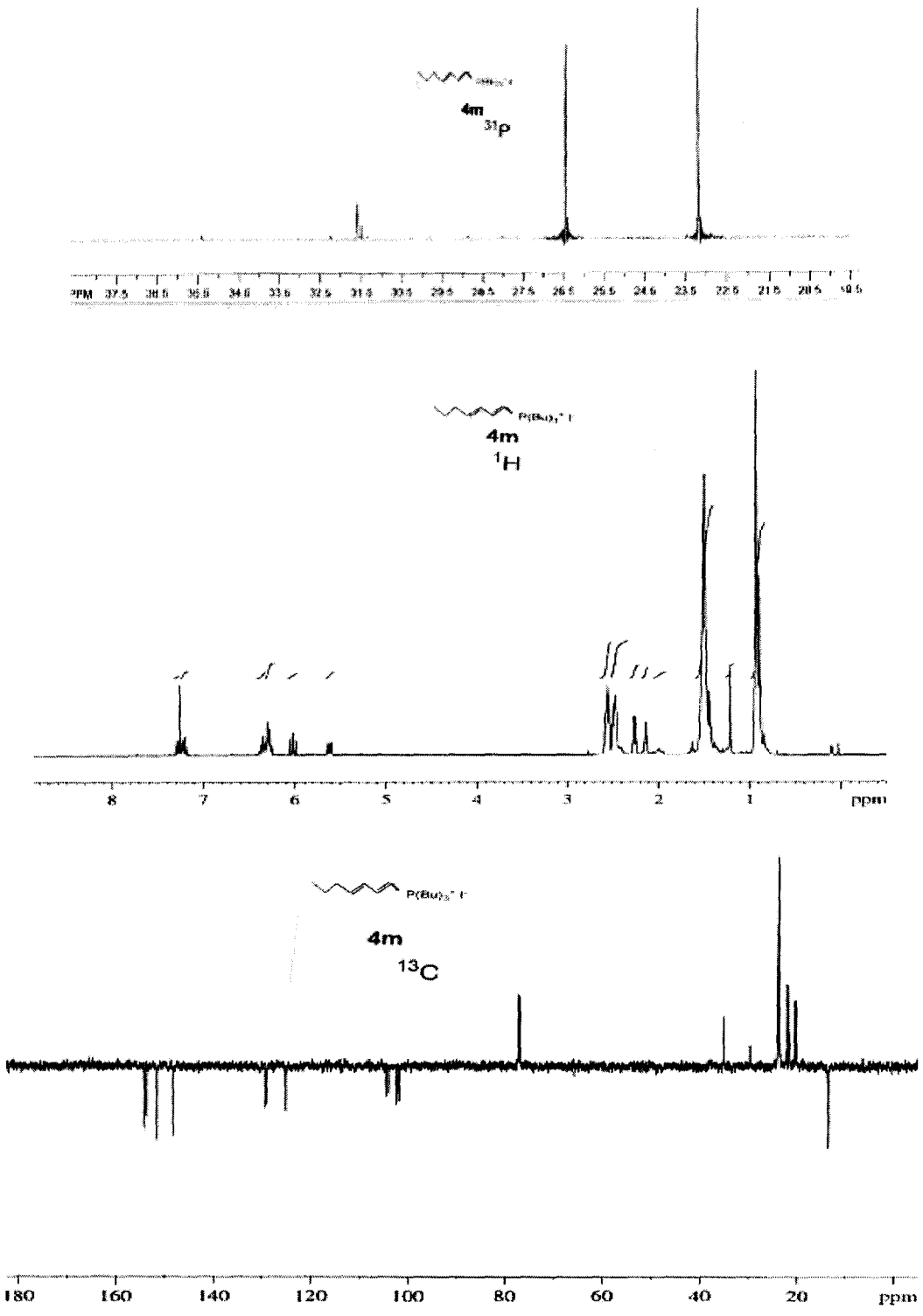

4j
13C
160
140
120
100
80
60
40
20
ppm


4k
31P


4k
1H


4k
13C


4l
31P
100
50
0
-50
-100
-150
4l
1H
4l
13C
180
160
140
120
100
80
60
40
20
ppm

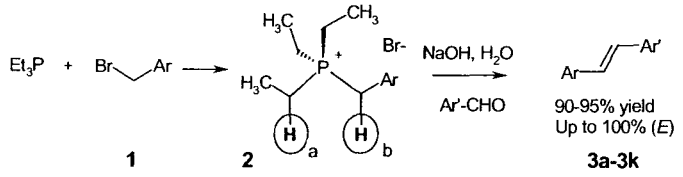

4m
31P
4m
1H
8
7
6
5
4
3
2
1
ppm
4m
13C
180
160
140
120
100
80
60
40
20
ppm

Chapter V

Highly stereoselective and general synthesis of *trans*-stilbenes and alkenes by means of an aqueous Wittig reaction

Introduction:

The Wittig reaction[1] has evolved over the last half-century to become one of the most strategic, widely-applicable carbon-carbon olefin bond forming processes available in organic synthesis.[2-4] This highly reliable reaction allows for olefination with complete positional selectivity, relatively high chemoselectivity and may be conducted in many cases with reliable and high stereocontrol. The reaction has been the subject of extensive experimental[2-5] and theoretical[5a] investigations and has been comprehensively reviewed.[2,4,5b] Two major drawbacks of the reaction are the lack of stereocontrol achieved in certain cases, for example in the synthesis of valuable stilbenes from semi-stabilized ylides,[6] and the practical issue of phosphane oxide side-product removal.



Scheme 1. Synthesis of stilbenes **3a-3k** using aqueous Wittig chemistry

Principal methods for the synthesis of stilbenes involve the Wittig[6-7] reaction for *cis*-stilbenes and the Wittig-Horner olefination reaction for *trans*-stilbenes.[6b,c] Both reactions typically require the use of dry organic solvents under inert conditions using a strong, non-aqueous base. The Wittig reaction employing a triphenylbenzyl ylide is still the most popular route to *cis*- and *trans*-stilbenes.[7] The process is typically high yielding but suffers from poor to moderate stereocontrol requiring both removal of the phosphane

oxide as well as separation of the stereoisomers. The use of water as a solvent for organic reactions is highly desirable for environmental, economical, safety and chemical processing reasons.[8,9] Significant rate-enhancements have also been observed using water as a medium for organic reactions.[10,11] Water has been used as the reaction medium for the Wittig reaction of stabilized ylides[12] giving unsaturated esters. The use of a triphenyl-substituted semi-stabilized ylide reacting with aromatic aldehydes has also been reported in water,[13] providing stilbenes with poor configurational selectivity and requiring chromatographic purification to remove triphenylphosphane oxide. Further advances involving the use of carboxyl- and sufonyl-substituted Wittig reagents in water and methanol have been reported.[14] These methods allow for easier phosphane oxide removal, however the funtionalized triarylphosphanes employed require multi-step syntheses and stereocontrol in the Wittig reaction is quite low.

Surprisingly, the Wittig reaction of semi-stabilized ylides derived from trialkylbenzyl phosphonium salts (such as **2**, Scheme 1) containing small alkyl groups has never been investigated in water. This may be due to the perception that chemoselective ylide formation involving deprotonation at the benzylic site (position b) over the six available α-alkyl protons (position a) would not be possible. Were this chemoselectivity possible, a successful demonstration of the chemistry outlined in Scheme 1 in water could allow for an environmentally benign and direct solution to two of the unresolved issues inherent to the classic Wittig reaction. The use of trialkylphosphane-derived ylides in Wittig olefination is of limited applicability but typically provides a higher ratio of *trans*-olefins.[4] Phosphane oxides containing small alkyl groups, such as trimethyl and triethylphosphane oxide, are highly soluble in water. Herein we report on the successful

achievement of these goals and advance a direct "green" totally organic solvent-free synthesis of *trans*-stilbenes and related olefins exclusively in aqueous media. Semi-stabilized triethylbenzylidenyl ylides are shown to be formed chemoselectively in water using sodium or lithium hydroxide; and these react with aromatic aldehydes in water, yielding *trans*-stilbenes with high stereocontrol. The entire process is conducted in water, and the product *trans*-stilbene is isolated by simple filtration and washing with water.

Trans-configured stilbenes constitute the central nucleus in a range of valuable materials including pharmaceuticals,[15-22] light emitting diodes[23] and dye-sensitized photo-voltaic solar cells.[24-27] In terms of pharmaceuticals, the stilbenes resveratrol and DMU-212 (**4** and **5**, Figure 1), have been shown to modulate diverse biological phenomena. Resveratrol **4**, a naturally occurring phytoalexin, has been associated with a diverse array of both cardiovascular and cancer preventative therapeutic effects including antioxidant, antiinflammatory, antiangiogenic, and antiestrogenic effects as well as its ability to induce apoptosis and many other specific enzyme inhibitory activities.[15-18] DMU-212 **5**, a synthetic derivative of resveratrol, was shown to be a more potent antiproliferative than resveratrol in human colon cancer cells.[19]

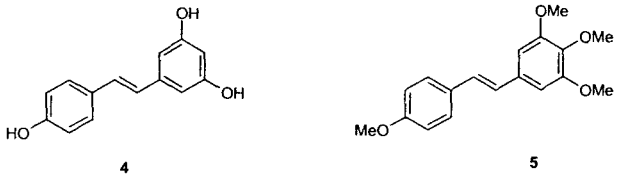
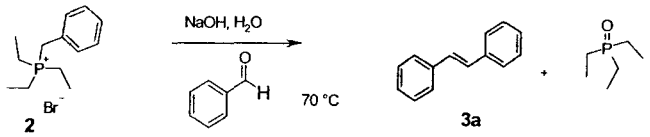


Figure 1. Structures of resveratrol **4** and DMU-212 **5**

Other valuable *trans*-stilbenes have recently been shown to bind to myelin and to be useful as molecular imaging probes in positron emission tomography (PET) in the diagnosis of disorders such as multiple sclerosis.[20-22] *Trans*-configured stilbenes are also

key components in both light emitting diodes (LEDs)[23] and photo-voltaic solar cells.[24] For example, electron-transporting *trans*-stilbenes have recently been shown to be the key components in improved electroluminescent donor-acceptor polymeric LEDs.[23] The development of efficient photoelectrochemical cells is regarded as one of the most challenging areas facing science.[25] The potential of photoelectrochemical cells in both the direct conversion of sunlight into electrical energy,[26] and in mediating the conversion of water to hydrogen and oxygen is immense.[27] A new class of dye-sensitized solar cell has recently emerged incorporating a donor-acceptor *trans*-stilbene as the light harvesting chromophore.[24]

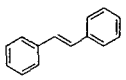
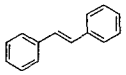
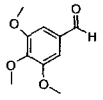
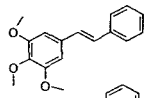
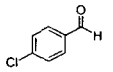
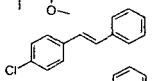
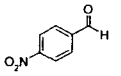
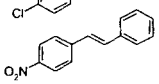
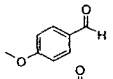
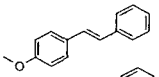
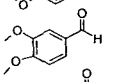
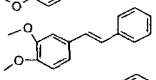
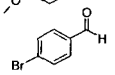
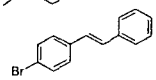
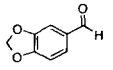
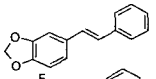
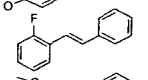
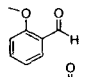
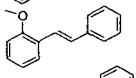
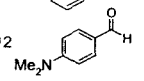
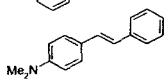


Scheme 2. Synthesis of stilbene **3a** via the aqueous Wittig reaction

Results and Discussion:

A model reaction involving the synthesis of unsubstituted *trans*-stilbene **3a** was first investigated and is shown in Scheme 2. Triethylbenzyl phosphonium bromide **2** was prepared *in-situ* through the direct 1:1 reaction of triethylphosphane with benzyl bromide. The salt was dissolved in water and sodium hydroxide and benzaldehyde were added yielding an emulsion. Upon warming, the product *trans*-stilbene slowly precipitated from solution. The reaction rate proved dependent on the concentration of sodium hydroxide and phosphonium salt. We settled upon the use of 4.0 equivalents of NaOH and a salt concentration of 2.5 M as a standard condition. From this reaction *trans*-stilbene **3a** was isolated in 99% yield and with 4:1, (*E*):(*Z*) stereoselectivity through simply cooling the aqueous suspension, filtering and washing with water. NMR analysis showed the solid

product to be free from triethylphosphane oxide and demonstrated that 1-phenylpropene was not formed, indicating high chemoselectivity in the ylide formation through benzylic CH deprotonation. We also note that no Cannizzaro side products were detected as might have been anticipated under these basic conditions. This same reaction conducted using lithium hydroxide provided *trans*-stilbene **3a** in 99% yield and a selectivity of 99:1(*E*):(*Z*), Table 1, entry 2.

Entry	ArCHO	Stilbene	% Yield	E:Z
1		 **3a**	99	80 : 20
2		 **3a**	99[a]	99 : 1
3		 **3b**	97	95 : 5
4		 **3c**	99	90 : 10
5		 **3d**	99	80 : 20
6		 **3e**	98	95 : 5
7		 **3f**	98	95 : 5
8		 **3g**	98	90 : 10
9		 **3h**	97	95 : 5
10		 **3i**	99	90 : 10
11		 **3j**	98	95 : 5
12		 **3k**	99	99 : 1

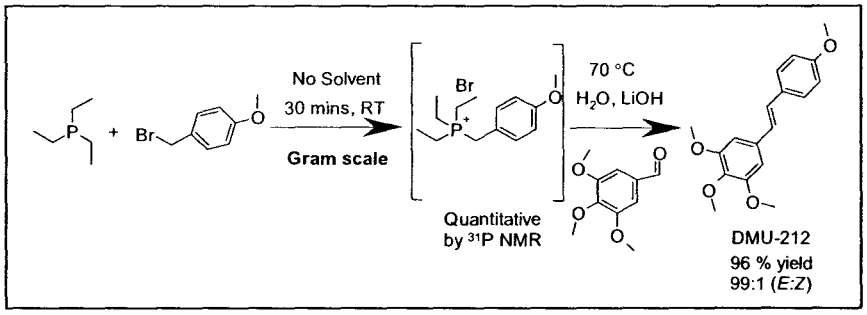
[a] LiOH was used as base.

Table 1. Synthesis of stilbene derivatives from reaction of various aldehydes.

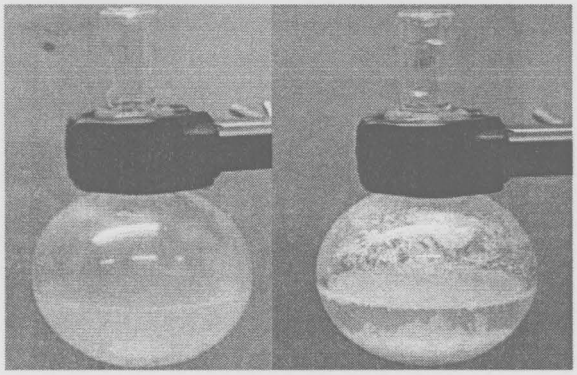
This aqueous Wittig reaction proved to be very general. The ylide formed *in-situ* from triethylbenzylphosphonium bromide in purely aqueous base reacted successfully with a

wide range of aldehydes exhibiting varying electronic and steric demands as shown in Table 1. Product yields are almost quantitative in all cases investigated so far. Stereoselectivity is high favouring the *trans*-stilbene isomer although electron withdrawing groups on the aldehyde appear to lower this stereoselectivity somewhat.

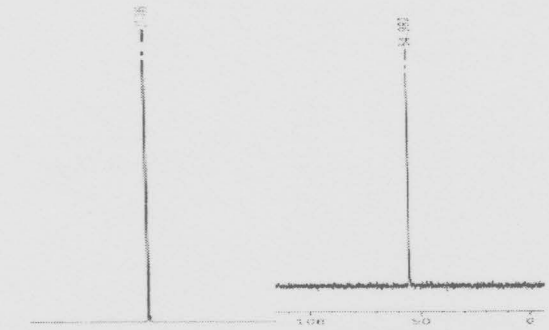
The synthesis of both resveratrol **4** and DMU-212 **5** was readily achieved through the analogous process employing the reaction of triethylphosphane with 4-methoxybenzyl bromide, under solvent-free conditions, which provided the 4-methoxyphenyl salt **2b**. Dissolving in aqueous sodium hydroxide (2.5 M) and addition of 3,5-dimethoxybenzaldehyde followed by warming to 70 °C for 3h, chilling, suction filtration and washing with water yielded the trimethyl ether of resveratrol in 95% yield and with an (*E*):(*Z*) ratio of 95:5. Demethylation with BBr_3 then gave resveratrol **4** in 80% yield (m.p. 256-258 °C).[28] Likewise, reaction of the basic solution of **2b** with 3,4,5-trimethoxybenzaldehyde (70 °C, 3- h), cooling, filtering and washing with water providing a gram-scale synthesis of the potent anticancer agent DMU-212 **5** directly in 96% isolated yield and (*E*):(*Z*) ratio of 99:1.[29]



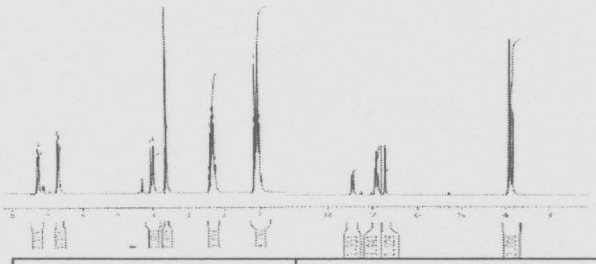
Scheme 2: Synthesis of DMU-212



2A. Phosphonium salt **2b** in water	**2B**. Final reaction mixture.



2C ^{31}P- NMR of Phosphonium salt in water	**2D** ^{31}P- NMR of aqueous phase after filtration



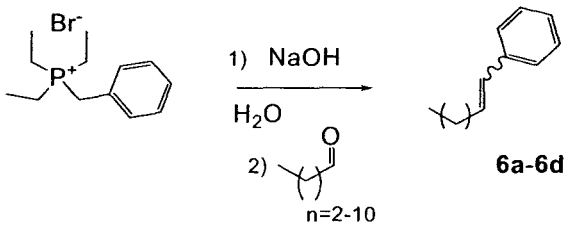
2E. ^{1}H-NMR of salt **2**	**2F**. ^{1}H-NMR of the crude precipitate after filtration.

Figure 2. Snapshots of the synthesis of DMU-212.

Figure 2 demonstrates the appearance of the reaction at various stages. The salt **2b** is formed cleanly (δ ^{31}P = 37.4 ppm, Fig. **2C**; ^{1}H-NMR, Fig. **2E**). The salt (2.5 M) and LiOH (4.0 eq) form a slightly cloudy aqueous solution (Fig. **2A**). Figure **2B** shows the appearance after the reaction. The resulting NMR spectra are reproduced below of the aqueous solution (Fig. **2D**) showing triethylphosphane oxide (δ ^{31}P = 54.9 ppm) and the filtered solid showing essentially the pure *trans*-stilbene DMU-212 **5** (Fig. **2F**) with no cross-contamination. No purification is required to remove triethylphosphane oxide from the stilbene in all cases investigated (Table 1) so far.

The aqueous Wittig reaction was also successfully extended to reaction with enolizable aliphatic aldehydes. At the outset, a major concern was the possibility of a competing Cannizzaro and/or homo-aldol reaction of such aldehydes, given that the reaction is performed under classic conditions known to effect these processes. Nonetheless, addition of NaOH to a suspension of butanal in the presence of triethylbenzyl phosphonium bromide **2** provided 1-phenyl-1-pentene **6a** (Table 2, entry 1) as the major product. Traces of polar products were observed, however chromatographic purification gave the olefin in 65% isolated yield. The process was successfully extended to a series of aliphatic aldehydes to give **6a-6d**. Interestingly, both isolated yield and (*E*)-olefin content increased proportionately with the aliphatic chain length. We attribute the higher yields to a lipophilic effect possibly involving micelles (*vide infra*). The higher (*E*)-olefin stereoselectivity is likely due to enhanced reactivity via the *trans*-oxaphosphetane intermediate.

Although the mechanism of the aqueous Wittig reaction is speculative, we note the formation of an emulsion from the suspension of the phosphonium salt and aldehyde in water. No reaction occurs until the base is added. The emulsion slowly disappears and the product precipitates. We connect these observations to the remarkable chemoselectivity



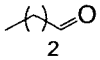
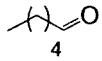
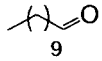
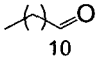
Aldehyde	yield	(*E*):(*Z*)
 2	65	2:3
 4	70	6.2:3.8
 9	72	7:3
 10	77	3:1

Table 2. Synthesis of 1-Phenylalkenes from enolizable aliphatic aldehydes

that is observed. Cannizarro and homo-aldol products are suppressed with both reactive aliphatic and aromatic aldehydes in the presence of classic reagents for these reactions. We believe that these results are most likely due to the formation of micelles, surface stabilized by the phosphonium salt, partitioning the organic materials from the aqueous basic environment. This partitioning is the most likely explanation for protection of the aldehyde from the expected basic side reactions. The aldehyde is subject to a locally selective reaction environment with the in-situ generated ylide. Rapid and reversible ylide generation occurs through deprotonation of the phosphonium salt occurs at the interface.

The neutral dipolar ylide is translocated to the lipophilic interior where the Wittig reaction takes place. The water-soluble phosphine oxide would be expected to diffuse out of the micelles to the aqueous phase. Precipitation or crystallization of the olefin product occurs as its concentration accumulates to the saturation point within the micelle. As the reaction nears completion and phosphonium salt and aldehyde are consumed, the micelles disappear leaving only a suspension of the olefin in water.

Conclusion:

In conclusion, we show that semi-stabilized ylides can be formed solely in aqueous media from the reaction of a trialkylbenzyl phosphonium salt and a metal hydroxide and that these ylides react with aromatic aldehydes in water to precipitate *trans*-stilbenes with high selectivity. As the triethylphosphane oxide side product is water soluble, we also show that the *trans*-stilbene product can be isolated in pure form simply by filtration and washing with water. The same ylides react with enolizable aliphatic aldehydes providing 1-phenylalkenes with good selectivity. Overall, this direct, high yielding synthesis of *trans*-stilbenes and alkenes in aqueous media is technically simple, general and provides high yields

of valuable pharmacological and photoactive materials with high configurational selectivity under environmentally benign conditions. In fact, the aqueous stilbene synthesis elevates the Wittig reaction of semi-stabilized ylides into the realm of "Click" chemistry, satisfying most of the stringent criteria.[30] Extension of the scope of the aqueous Wittig chemistry and mechanistic investigations are under study.

References:

1. Wittig, G.; Geissler, G. *Liebigs Ann Chem.* **1953**, 580, 44-57.
2. Takeda, T. *Modern Carbonyl Olefination*, Wiley-VCH, Weinheim, **2004**.
3. Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, 21, 1-157.
4. Maryanoff, B. E.; Reitz, A. B. *Chem Rev.* **1989**, 89, 863-927.
5. (a) Robiette, R.; Richardson, J.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2006**, 128, 2394-2409. (b) Edmonds, M.; Abell, A. in *Modern Carbonyl Olefination*, (Ed. T. Takeda), Wiley-VCH, Weinheim, **2004**, pp 1-17.
6. (a) Orsini, F.; Verotta, L.; Lecchi, M.; Restano, R.; Curia, G.; Redaelli, E.; Wanke, E. *J. Nat. Prod.* **2004**, 67, 421-426. (b) Cushma, M.; Dhanapalan, N.; Gopal, D.; Chakraborti, A. K.; Lin, C. M.; Hamel, E. *J. Med Chem.* **1991**, 34, 2579-2588. (c) Simoni, D.; Roberti, M.; Invidiata, F. P. *Bioorg. & Med. Chem. Lett.* **2006**, 16, 3245-3248.
7. (a) Pettit, G. R.; Thornhill, A.; Melody, N.; Knight, J. C. *J. Nat. Prod.* **2009**, 72, 380-388. (b) Shirali, A.; Sriram, M.; Hall, J. J.; Nguyen, B. L.; Guddneppanavar, R.; Hadimani, M. B.; Ackley, J. F.; Siles, R.; Jelinek, C. J.; Arthasery, P.; Brown, R. C.; Murrell, V. L.; McMordie, A.; Sharma, S.; Chaplin, D. J.; Pinney, K. G. *J. Nat. Prod.* **2009**, 72, 414-421.
8. Li, C. J. *Chem. Rev.* **1993**, 93, 2023-2035.
9. Lindstrom, U. M. *Chem. Rev.* **2002**, 102, 2751-2772.
10. Naraya, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, 44, 3275-3279.
11. Klijn, J. E.; Engberts, J. B. F. N. *Nature* **2005**, 435, 746-747.

12. (a) Dambacher, J.; Zhao, W.; El-Batta, A.; Anness, R.; Jiang, C.; Bergdahl, M. *Tetrahedron Lett.* **2005**, 46, 4473-4477; (b) Orsini, F.; Sello, G.; Fumagalli, T. *Synlett* **2006**, 1717-1718. (c) Molander, G. A.; Oliveira, R. A. *Terahedron Lett.* **2008**, 49, 1266-126.

13. Wu, J.; Li, D.; Zhang, D. *Synth. Commun.* **2005**, 35, 2543-2551.

14. (a) Russel, M. G.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 505-513. (b) Huo, C.; He, X.; Chan, T. H. *J. Org. Chem.* **2008**, 73, 8583-8586.

15. Aggarwal, B. B.; Bhardwaj, A.; Aggarwal, R. S.; Seeram, N. P.; S. Shishodia, S.; Takada, Y. *Anticancer Res.* **2004**, 24, 2783-2840.

16. Saiko, P.; Szakmary, A.; Jaeger, W.; Szekres, T. *Mutation Res.* **2008**, 658, 68-94.

17. Sale, S.; Verschoyle, R. D.; Boocock, D.; Jones, D. J. L.; Wilsher,N.; Ruparelia, K. C.; Potter, G. A.; Farmer, P. B.; Steward, W. P.; Gescher, A. J. *Br. J. Cancer* **2004**, 90, 736-744.

18. Baur, J. A.; Sinclair, D. A. *Nature Rev.* **2006**, 5, 493-506.

19. Sale, S.; Tunstall, R. G.; Ruparelia, K. C.; Potter, G. A.; Steward, W. P.; Gescher, A. J. *Int. J. Cancer* 2005, 115, 194-201.

20. Wu, C.; Wei, J.; Tian, D.; Feng, Y.; Miller, R. H.; Wang, Y. *J. Med. Chem.* **2008**, 51, 6682-6688.

21. Stankoff, B.; Wang, Y.; Bottlaender, M.; Aigrot, M. S.; Dolle, F. *Proc. Natl. Acad. Sci. USA* **2006**, 103, 9304-9309.

22. Wu, C.; Tian, D.; Feng, Y.; Polak, P.; Wei, J. *J. Histochem. Cytochem.* **2006**, 54, 997-1004.

23. Xun, S.; Zhou, Q.; Li, H.; Ma, D.; Wang, L.; Jing, X.; Wang, F. *J. Pol Sci, Pt. A, Polym. Chem.* **2008**, 46, 1566-1576.

24. Kim, C.; Choi, H.; Kim, S.; Baik, C.; Song, K.; Kang, M. S.; Kang, S. O.; Ko, J. *J. Org. Chem.* **2008**, 73, 7072-7079.

25. Kerr, R. A.; Service, R. F. *Science* **2005**, 309, 101.

26. Nazeeruddin, M. K.; De Angelis, F.; Fantacci, S.; Selloni, A.; Viscardi, G.; Liska, P.; Ito, S.; Takeru, B.; Grätzel, M. *J. Am. Chem. Soc.* **2005**, 127, 16835-16847.

27. Grätzel, M. *Nature* **2001**, 414, 338-344.

28. Koh, D.; Park, K. W.; Jung, J.; Yang, H.; Mok, K. H.; Lim, Y. *Magn. Res. Chem.* **2001**, 39, 768-770.

29. Robinson, J. E.; Taylor, R. J. K. *Chem. Commun.* **2007**, 1617-1619.

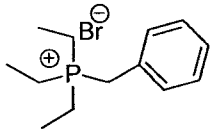
30. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, 40, 2004-2021.

Experimental:

General Information:

Reactions were carried out under air in oven-dried glassware. All fine chemicals were obtained from Aldrich except triethylphosphine, tributylphosphine and triisobutylphosphine, which were obtained from Cytec industries. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV and HRMS (EI) were performed with a Micromass Q-Tof Ultima spectrometer. ^{1}H, ^{13}C and ^{31}P spectra were recorded on Bruker 200, AV 600 and AV 700 spectrometers in $CDCl_3$ with TMS as internal standard, chemical shifts (δ) are reported in ppm downfield of TMS and coupling constants (J) are expressed in Hz. Signal assignments were accomplished *via* analysis of HMBC, HMQC, COSY, and NOESY experiments where necessary. The (*E*) to (*Z*) ratios were determined from the relative integration of the ^{1}H NMR spectra for the olefinic protons.

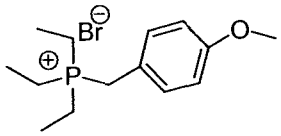
Benzyl-triethylphosphonium-bromide:



Into a flame dried flask triethylphosphine (500 µL, 3.40 mmol) was dissolved in dry DCM (3.4 mL) under argon and cooled at 0°C. Benzylbromide (404 µL, 3.40 mmol) was added via syringe. The solution was warmed to room temperature and stirred for 1 h. The DCM was evaporated under vacuum to yield the title compound in 99% yield (973.4 mg) as white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.12 (m, 9H), 2.47 (m, 6H), 4.14 (d, J_{PH} = 15.4 Hz, 2H), 7.24 (m, 3H), 7.39 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 6.0, 12.0 (d,

J_{PC} = 47.9 Hz), 26.0 (d, J_{PC} = 44.6 Hz), 128.3, 129.4, 130.2; ^{31}P-NMR (80 MHz, $CDCl_3$): 35.8; HRES MS $(M)^+$ calcd. for $C_{13}H_{22}P$: 209.1459, found 209.1466.

4-Methoxybenzyl-triethylphosphonium-bromide:

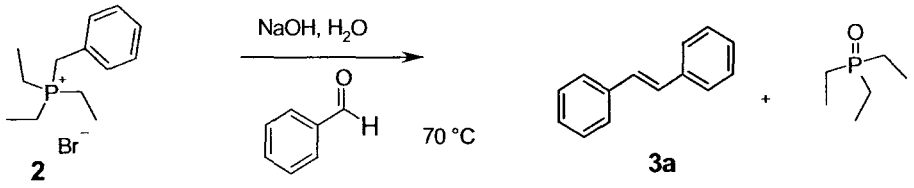


Into a flame dried flask triethylphosphine (500 μL, 3.40 mmol) was dissolved in dry DCM under argon and cooled at 0 °C. Then 4-methoxybenzylbromide (489.4 μL, 3.40 mmol) was added via syringe. Then the solution was warmed to room temperature and stirred for 1h. The DCM was evaporated under vacuum to yield the title compound in 98% yield (1.06 g) as white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.12 (m, 9H), 2.35 (m, 6H), 3.67 (s, 3H), 4.04 (d, J_{PH} = 14.6 Hz, 2H), 6.74 (m, 3H), 7.30 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 6.0, 11.9 (d, J_{PC} = 47.9 Hz), 25.1 (d, J_{PC} = 45.1 Hz), 55.3, 114.8, 129.3, 131.3, 159.5; ^{31}P-NMR (80 MHz, $CDCl_3$): 35.4; HRES MS $(M)^+$ calcd. for $C_{13}H_{24}OP$: 239.1573, found 239.1565.

General one pot procedure for Stilbene synthesis:

Into a flame dried flask was added triethylphosphine (1 eq) under argon at 0 °C. Benzylbromide (1 eq) was subsequently added via syringe (solvent free). The solution was warmed to room temperature slowly and stirred for 1h. To the phosphonium salt so formed was added the required amount of distilled water to make a 2.5 M solution. The mixture was stirred for 15 min at room temperature whereupon NaOH (4 eq) was added slowly. After 2 min the corresponding aldehyde (0.95 eq) was added slowly to the reaction flask. The mixture was stirred vigorously at 70 °C for 3 h. The oil bath was

removed and the flask was left to attain room temperature of its own accord. Water was added to the reaction mixture and the flask was stirred for 10 mins. The slurry was vacuum filtered and dried to yield the corresponding stilbene in pure form.



Base optimization (0.5M phosphonium salt):

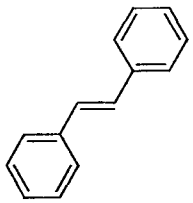
no of eq of base	conc	% conversion of benzaldehyde	Time
1	0.5	65	7 hrs
2	0.5	75	7 hrs
3	0.5	90	7 hrs
4	0.5	100	7 hrs

Phosphonium salt concentration:

no of eq of base	conc	time for 100 % conversion
4	0.5	7
4	1.0	6
4	2.0	4
4	2.5	3

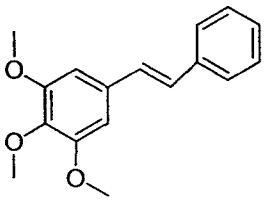
Optimization Study

(*E*)-1,2-diphenylethene 3a:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min benzaldehyde (192μL, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 15 mL water was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound **3a,** 338.7 mg, (99%) as white solid. Mp 122-124 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.13 (s, 2H), 7.27 (t, J_{HH} = 7.4 Hz, 2H), 7.38 (t, J_{HH} = 7.6 Hz, 4H), 7.54 (t, J_{HH} = 7.6 Hz, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 126.6, 127.7, 128.7, 128.8, 137.3; HRCI MS $(M)^{+}$ calcd. for $C_{14}H_{12}$: 180.0944, found: 180.0939.

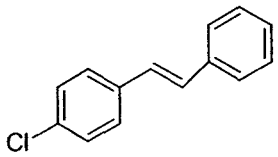
(*E*)-1,2,3-trimethoxy-5-styrylbenzene 3b:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to

make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min 3'4'5-trimethoxy-benzaldehyde (372.6 mg, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 15 mL water was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound **3b**, 498 mg, (97%) as light yellow solid. Mp 105-107 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.93 (s, 6H), 6.76 (s, 2H), 7.04 (s, 2H), 7.20 (m, 3H), 7.54 (d, J_{HH} = 7.5 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 56.2, 61.1, 103.6, 126.6, 127.7, 128.2, 128.8, 133.2, 137.3, 153.5; HRCI MS $(M)^{+}$ calcd. for $C_{17}H_{18}O_3$: 270.1249, found: 270.1256.

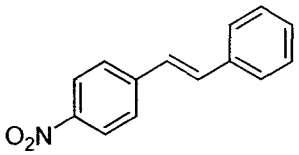
(*E*)-1-(4-chlorostyryl)-benzene 3c:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min 4-chlorobenzaldehyde (267.1 mg, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 15 mL water was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound **3c,** 402.6

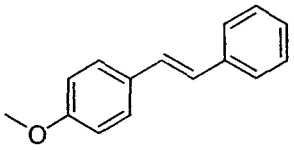
mg, (99%) as white solid. Mp 125-127 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.06 (s, 2H), 7.26-7.35 (m, 5H), 7.43 (d, J_{HH} = 8.5 Hz, 2H), 7.51 (d, J_{HH} = 7.3 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 126.6, 127.4, 127.7, 127.8, 128.7, 128.8, 129.3, 133.2, 135.8, 137.1; HRCI MS $(M)^+$ calcd. for $C_{14}H_{11}Cl$: 214.0552, found: 214.0549.

(*E*)-1-(4-nitrostyryl)-benzene 3d:



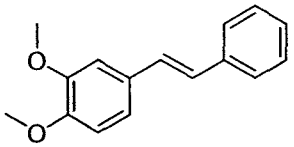
Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min 4-nitrobenzaldehyde (287.2 mg, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 15 mL water was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound **3d,** 423.4 mg, (99%) as brown solid. Mp 154-156 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.15 (d, J_{HH} = 16.7 Hz, 2H), 7.23-7.42 (m, 3H), 7.56 (d, J_{HH} = 7.3 Hz, 2H), 7.64 (d, J_{HH} = 8.7 Hz, 2H), 8.23 (d, J_{HH} = 8.7 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 124.0, 126.3, 126.9, 127.0, 128.8, 128.9, 129.0, 133.3, 136.2, 143.9, 146.8; HRCI MS $(M)^+$ calcd. for $C_{14}H_{11}NO_2$: 225.0779, found: 225.0790.

(*E*)-1-(4-methoxystyryl)-benzene 3e:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min 4-methoxybenzaldehyde (230.4 μL, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 15 mL water was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound **3e,** 391.2 mg, (98%) as white solid. Mp 135-136 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.91 (d, J_{HH} = 8.9 Hz, 2H), 7.0 (d, J_{HH} = 16.3 Hz, 1H), 7.10 (d, J_{HH} = 16.3 Hz, 1H), 7.26 (t, J_{HH} = 7.3 Hz, 1H), 7.35 (t, J_{HH} = 7.6 Hz, 2H), 7.45-7.54 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 55.3, 114.1, 126.7, 126.3, 127.2, 127.8, 128.3, 128.6, 130.2, 137.6, 159.3; HRCI MS $(M)^{+}$ calcd. for $C_{15}H_{14}O$: 210.1041, found: 210.1045.

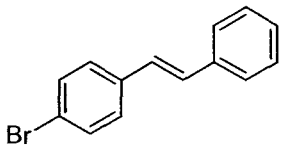
(*E*)-1,2-dimethoxy-4-styrylbenzene 3f:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min 3'4-dimethoxybenzaldehyde

(315.7 mg, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 15 mL water was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound **3f,** 447.1 mg, (98%) as white solid. Mp 107-108 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.94 (s, 3H), 6.85 (d, J_{HH} = 8.0 Hz, 1H), 6.97 (d, J_{HH} = 16.2 Hz, 1H), 7.05 (m, 3H), 7.24 (m, 1H), 7.35 (m, 2H), 7.47 (d, J_{HH} = 7.5 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 55.9, 56.0, 108.7, 111.2, 120.0, 126.3, 126.9, 127.4, 128.5, 128.7, 130.5, 137.6, 149.9, 149.2; HRCI MS $(M)^{+}$ calcd. for $C_{16}H_{16}O_2$: 240.1148, found: 240.1150.

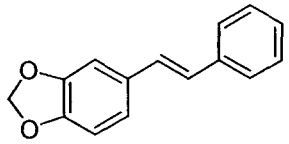
(*E*)-1-(4-bromostyryl)-benzene 3g:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min 4-bromobenzaldehyde (351.6 mg, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 15 mL water was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound **3g,** 480.4 mg, (98%) as white solid. Mp 126-127 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.04 (s, 2H), 7.16-7.32 (m, 5H), 7.36-7.52 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 121.5, 126.8,

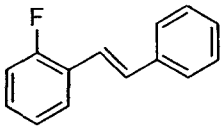
127.5, 128.1, 128.2, 129.0, 129.5, 132.0, 136.5, 137.0; HRCI MS $(M)^+$ calcd. for $C_{14}H_{11}Br$: 258.0049, found: 258.0044.

(*E*)-5-styrylbenzo[d][1,3]dioxole 3h:



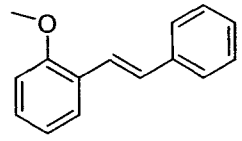
Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min piperonal (285.3 mg, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 15 mL water was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound **3h,** 413.0 mg, (97%) as white solid. Mp 88-90 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.93 (s, 2H); 6.78 (d, J_{HH} = 8.5 Hz, 1H), 6.91 (d, J_{HH} = 16.3 Hz, 1H), 6.92 (dd, d, J_{HH} = 8.5 Hz, 1H), 7.01 (d, J_{HH} = 16.3 Hz, 1H), 7.05 (s, 1H), 7.22 (d, J_{HH} = 7.2 Hz, 1H), 7.32 (t, d, J_{HH} = 7.2 Hz, 2H), 7.45 (d, J_{HH} = 7.2 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 101.2, 105.6, 108.5, 121.6, 126.4, 127.1, 127.5, 128.4, 128.8, 132.0, 137.5, 147.4, 148.3; HRCI MS $(M)^+$ calcd. for $C_{15}H_{12}O_2$: 224.0838, found: 224.0837.

(*E*)-1-(2'-fluorostyryl)-benzene 3i:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min 2-fluorobenzaldehyde (199 μL, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 15 mL water was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound **3i,** 372.6 mg, (99%) as white solid. Mp 94-95 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.09 (ddd, J_{HH} = 1.2 Hz, 8.2 Hz, 10.8 Hz, 1H), 7.16 (t, J_{HH} = 8.3 Hz, 1H), 7.20 (d, J_{HH} = 16.8 Hz, 1H), 7.22-7.26 (m, 1H), 7.31 (m, 2H), 7.39 (t, J_{HH} = 7.8 Hz, 2H), 7.56 (d, J_{HH} = 7.2 Hz, 2H), 7.63 (dt, J_{HH} = 1.2 Hz, 7.8 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 115.8 (d, J = 21.9 Hz), 120.9, 124.2, 125.3 (d, J = 16.1 Hz), 126.7, 127.0, 128.8, 128.9, 130.9, 131.0, 137.2, 157.1; HRCI MS $(M)^{+}$ calcd. for $C_{14}H_{11}F$: 198.0845, found: 198.0848.

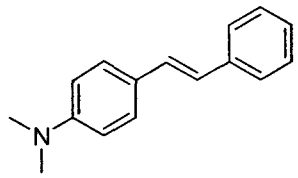
(*E*)-1-(2'-methoxystyryl)-benzene 3j:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min 2-methoxybenzaldehyde (230 μL, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at

70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 15 mL water was added to the reaction mixture and the flask was stirred for 10 mins. The slurry was vacuum filtered and dried to yield the title compound **3j,** 391.2 mg, (98%) as white solid. Mp 55-57 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 6.95 (d, J_{HH} = 8.2 Hz, 1H), 7.03 (t, J_{HH} = 7.6 Hz, 1H), 7.21 (d, J_{HH} = 16.7 Hz, 1H), 7.30-7.55 (m, 5H), 7.58-7.72 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 55.6, 111.1, 120.9, 123.6, 126.4, 126.6, 127.5, 128.8, 129.2, 138.1, 157.1; HRCI MS $(M)^{+}$ calcd. for $C_{15}H_{14}O$: 210.1044, found: 210.1045.

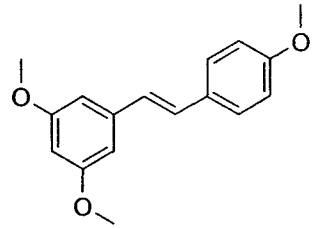
(*E*)-N,N-dimethyl-4-styrylbenzenamine 3k:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min 4-dimethylaminobenzaldehyde (283.7 mg, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 15 mL water was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound **3k,** 419.7 mg, (99%) as yellow solid. Mp 145-147 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.96 (s, 6H), 6.71 (d, J_{HH} = 8.2 Hz, 2H), 6.95 (d, J_{HH} = 16.3 Hz, 1H), 7.05 (d, J_{HH} = 16.3 Hz, 1H), 7.19 (t, J_{HH} = 7.3 Hz, 1H), 7.32 (t, J_{HH} = 7.5 Hz, 2H), 7.41 (d,

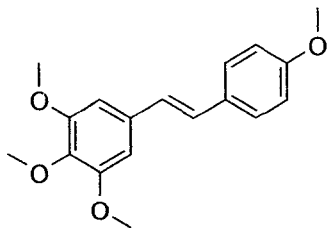
J_{HH} = 8.7 Hz, 2H), 7.47 (d, J_{HH} = 7.4 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 40.8, 112.9, 124.9, 126.5, 127.1, 128.0, 129.0, 129.2, 138.5, 150.3; HRCI MS $(M)^+$ calcd. for $C_{16}H_{17}N$: 223.1364, found: 223.1361.

1-(4-methoxystyryl)-3,5-dimethoxybenzene:



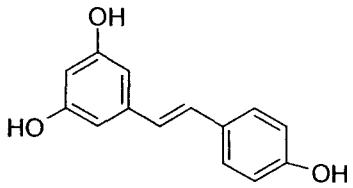
Into a flame-dried flask, containing a magnetic stirring bar, was weighed 4-methoxybenzyl-triethylphosphonium salt (100 mg, 0.42 mmol) and distilled water (0.17 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (67 mg, 1.7 mmol) was added slowly. After 2 min 3,5-dimethoxybenzaldehyde (66 mg, 0.4 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 6 mL water was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound, 103 mg, (95%) as white solid. The spectral data was identical to that reported[1]

5-(4-methoxystyryl)-1,2,3-trimethoxybenzene 5:



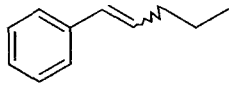
Into a flame-dried flask, containing a magnetic stirring bar, was weighed 4-methoxybenzyl-triethylphosphonium salt (100 mg, 0.42 mmol) and distilled water (0.17 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (67 mg, 1.7 mmol) was added slowly. After 2 min 3,4,5-trimethoxybenzaldehyde (78.5 mg, 0.4 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. Water (6 ml) was added to the reaction mixture and the flask was stirred for 10 min. The slurry was vacuum filtered and dried to yield the title compound DMU-212 **5,** 115.2 mg, (96%) as yellowish solid. The spectral data was identical to that reported[2]

(*E*)-5-(4-hydroxystyryl)benzene-1,3-diol (resveratrol) 4:



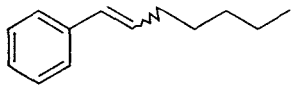
Into a flame dried flask the trimethoxystillbene (50 mg, 0.185 mmol) was dissolved in dry DCM under argon and cooled at –30 °C. Then BBr_3 (105 µL, 1.111 mmol) was added via syringe. Then the solution was warmed to room temperature and stirred for 2 h. Water (5 mL) was added slowly to the reaction mixture and stirred further for 30 min. The DCM was evaporated under vacuum and the water phase was extracted with ethyl acetate (10 mL X 3) and dried over Na_2SO_4. The solvent was removed under vacuum. The resulting solid was recrystallized from ethanol/water to yield brown crystals (34 mg, 80% yield). The compound was identical with a commercially available specimen (mp 256-258 °C, CAS Registry Number: 501-36-0).

1-(pent-1-enyl)benzene 6a:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min butanal (171 μL, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (Hexane) to yield the title compound **6a,** 180.3 mg, (65%) as colorless oil. The spectral data was identical to that reported[3]

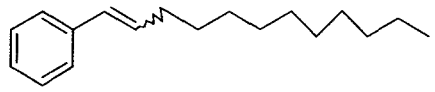
1-(hept-1-enyl)benzene 6b:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min hexanal (233.5 μL, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water

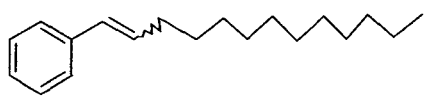
was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (Hexane) to yield the title compound **6b,** 231.6 mg, (70%) as colorless oil. The spectral data was identical to that reported[4]

1-(dodec-1-enyl)benzene 6c:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min undecanal (392 µL, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (Hexane) to yield the title compound **6c,** 334 mg, (72%) as colorless oil. The spectral data was identical to that reported[5]

1-(tridec-1-enyl)benzene 6d:

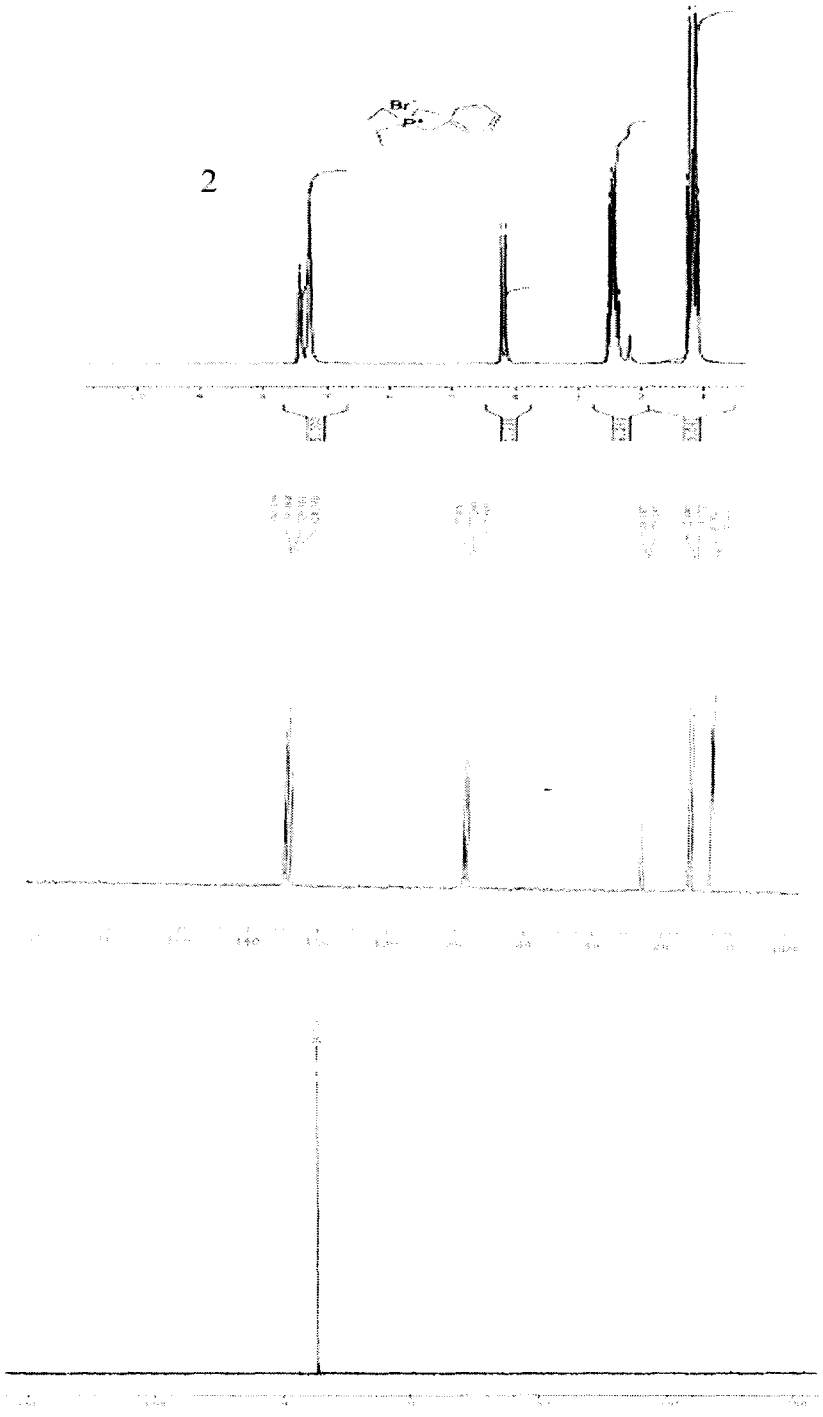


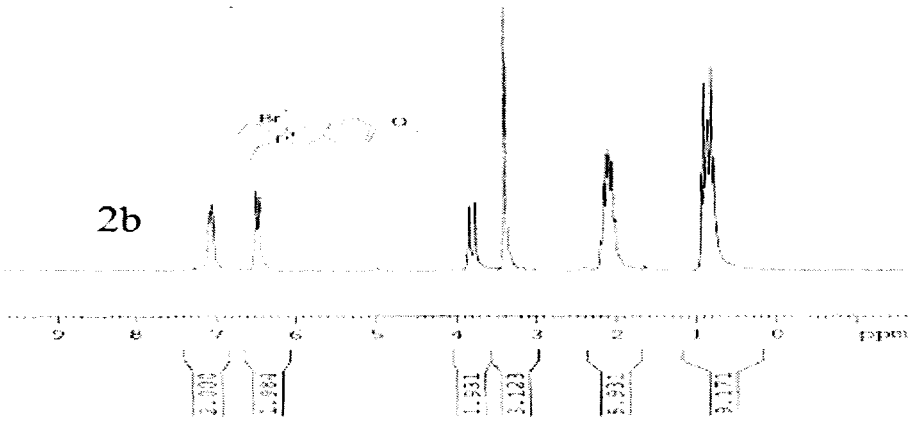
Into a flame-dried flask, containing a magnetic stirring bar, was weighed benzyl-triethylphosphonium salt (576.1 mg, 2 mmol) and distilled water (0.8 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (320 mg, 8.0 mmol) was added slowly. After 2 min dodecanal (421.4 μL, 1.9 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 3 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (Hexane) to yield the title compound **6d,** 377.8 mg, (77%) as colorless oil. The spectral data was identical to that reported[6]

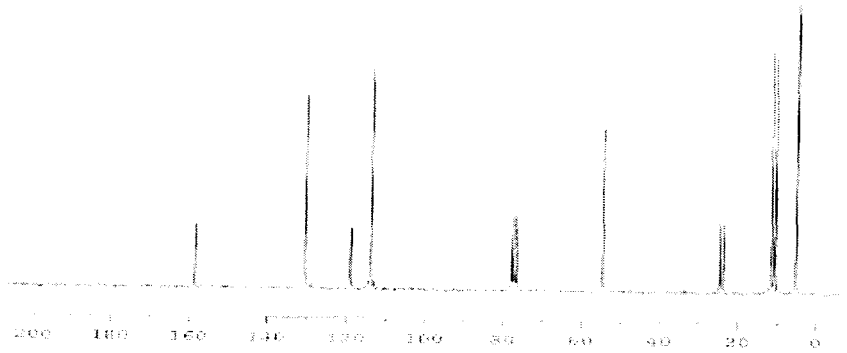
References (Experimental):

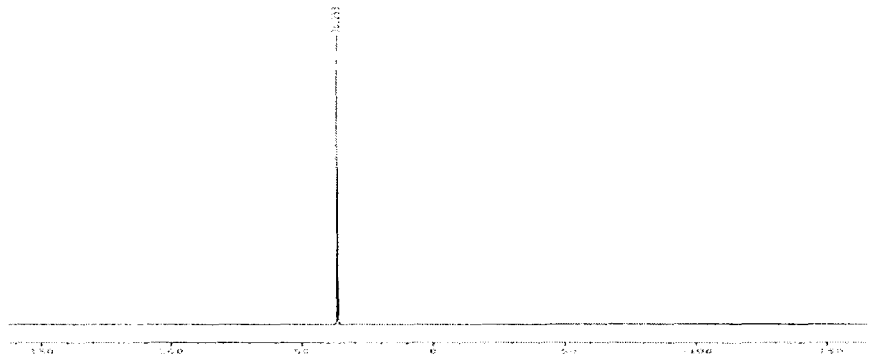
1. Koh, D.; Pārk, K. W.; Jung, J.; Yang, H.; Mok, K. H.; Lim, Y. *Magn. Reson. Chem.* **2001**, 39, 768-770.
2. Robinson, J. E.; Taylor, R. J. K. *Chem. Commun.* **2007**, 1617-1619.
3. Buss, A. D.; Warren. S. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2307-2325.
4. Denmark, S. E.; Kallemeyn, J. M. *J. Am. Chem. Soc.* **2006**, 128, 15958-15959.
5. Hodgson, D. M.; Fleming, M. J.; Stanway, S. J. *J. Am. Chem. Soc.* **2004**, 126, 12250-12251.
6. Habrant, D.; Stengel, B.; Meunier, S.; Mioskowski, C. *Chem. Eur. J.* **2007**, 13, 5433-5440.

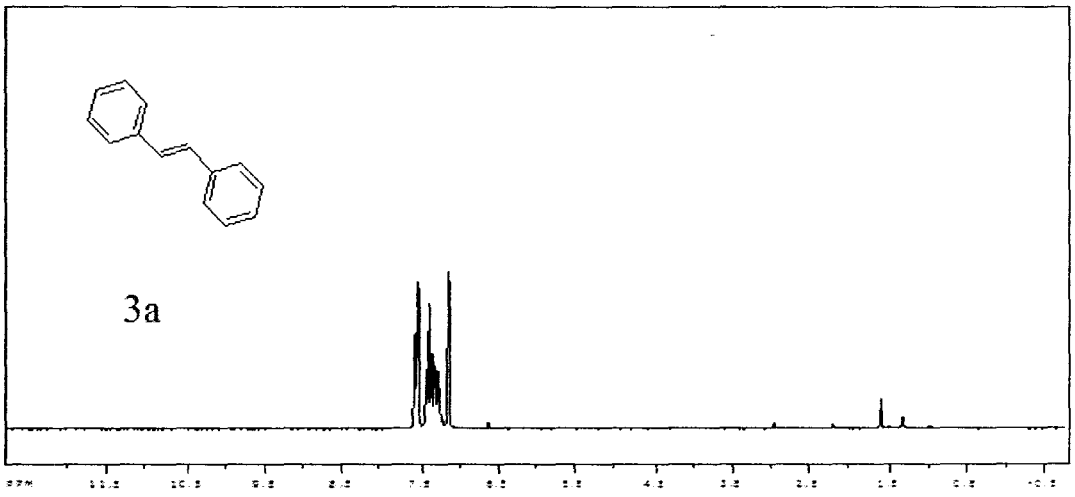
NMR Spectra of New Compounds:

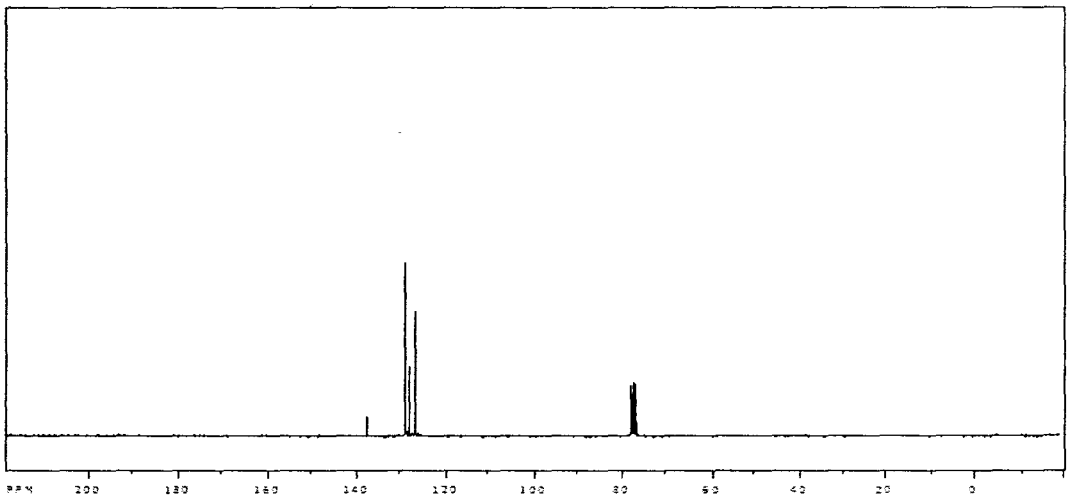


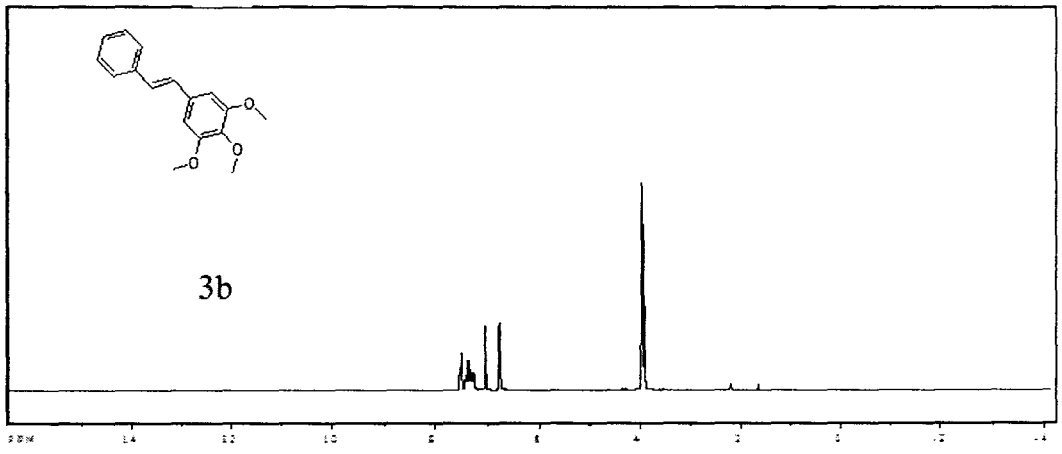

2b
9
8
7
6
5
4
3
2
1
0
ppm
2.000
4.084
1.331
3.123
2.231
9.115

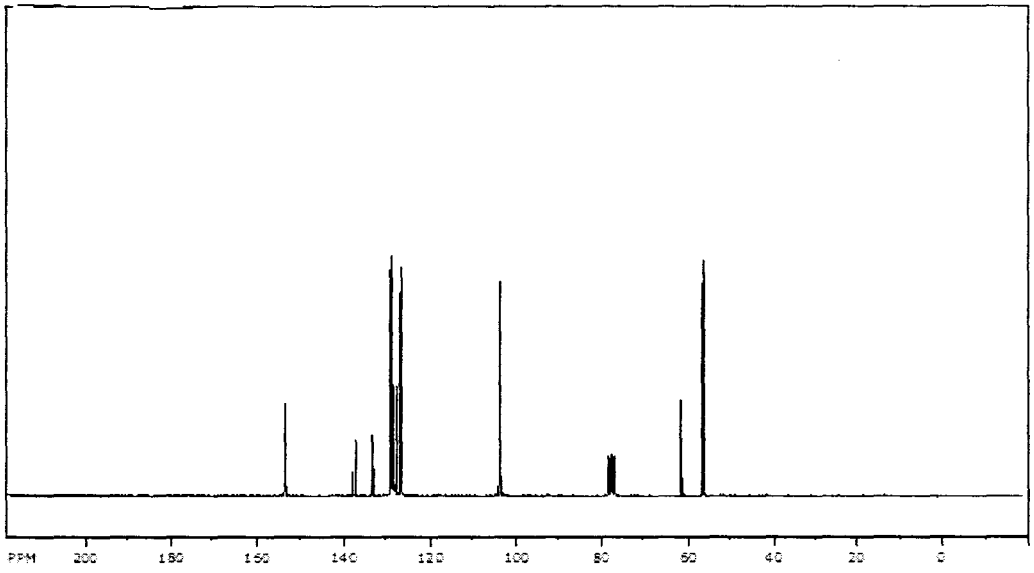

200
180
160
140
120
100
80
60
40
20
0

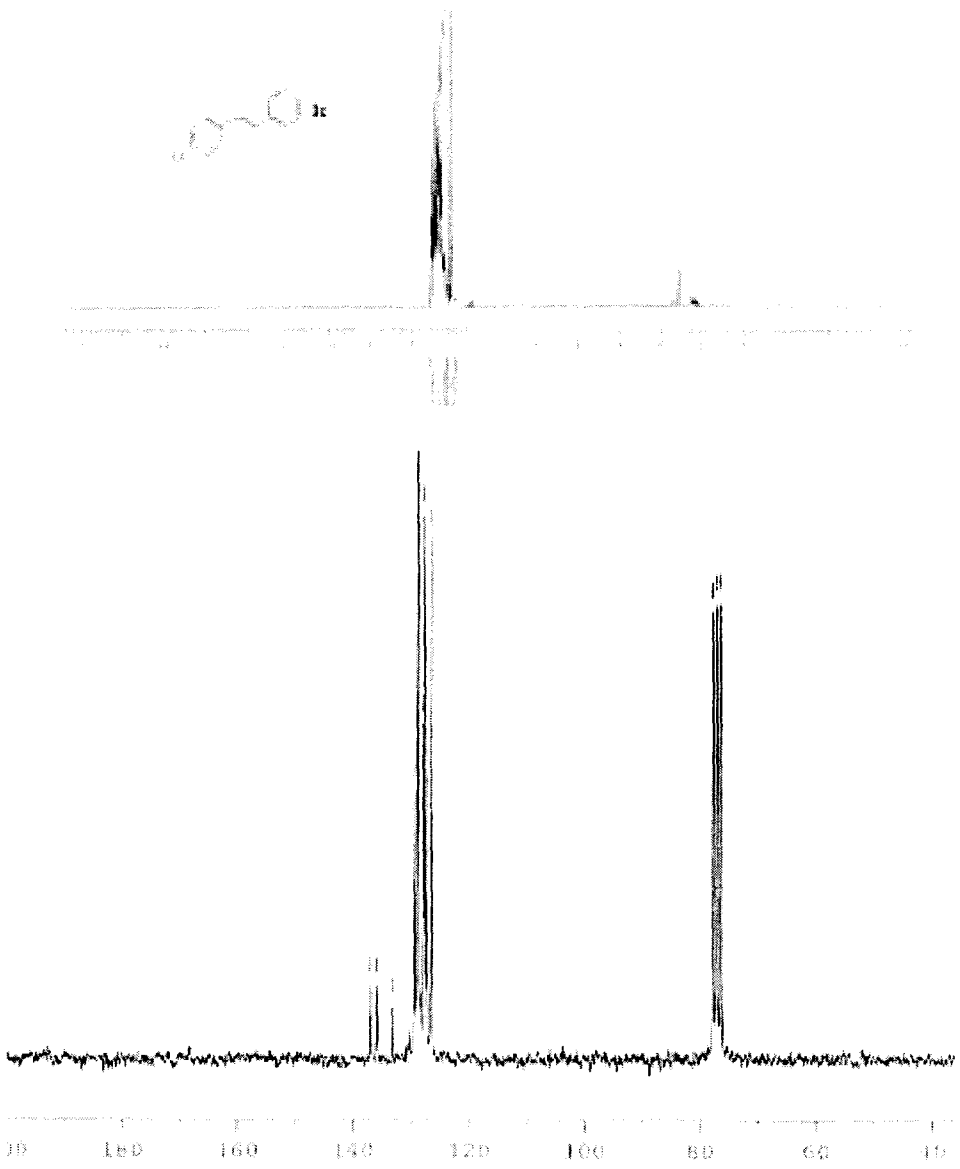


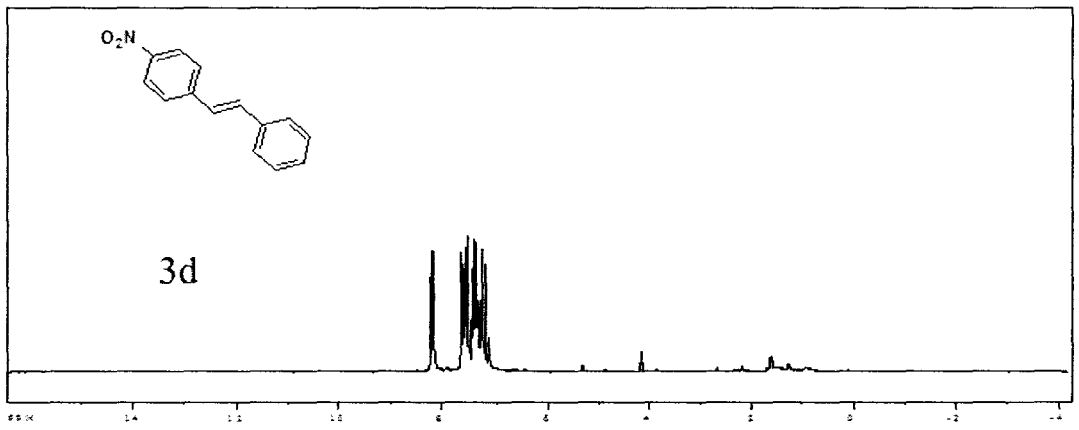

3a

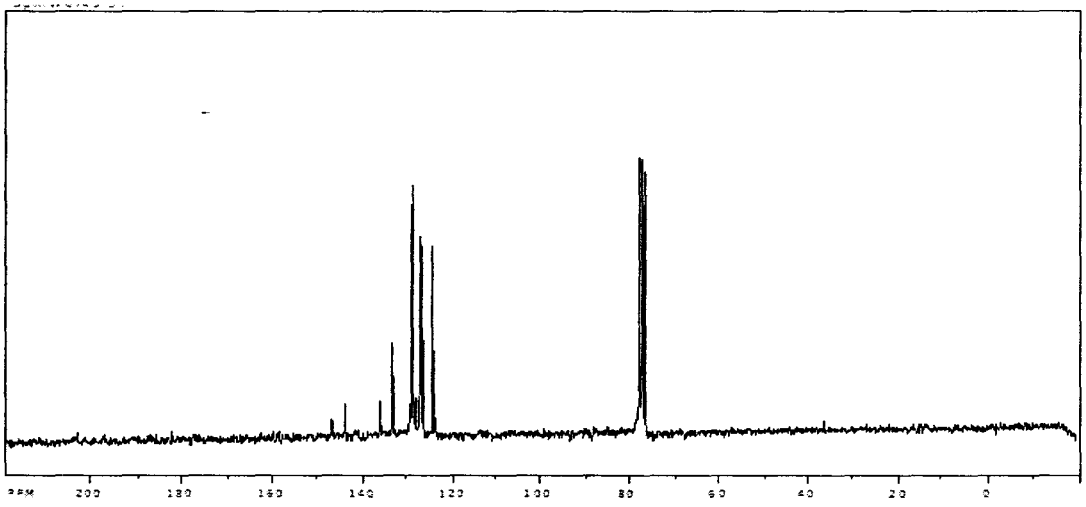


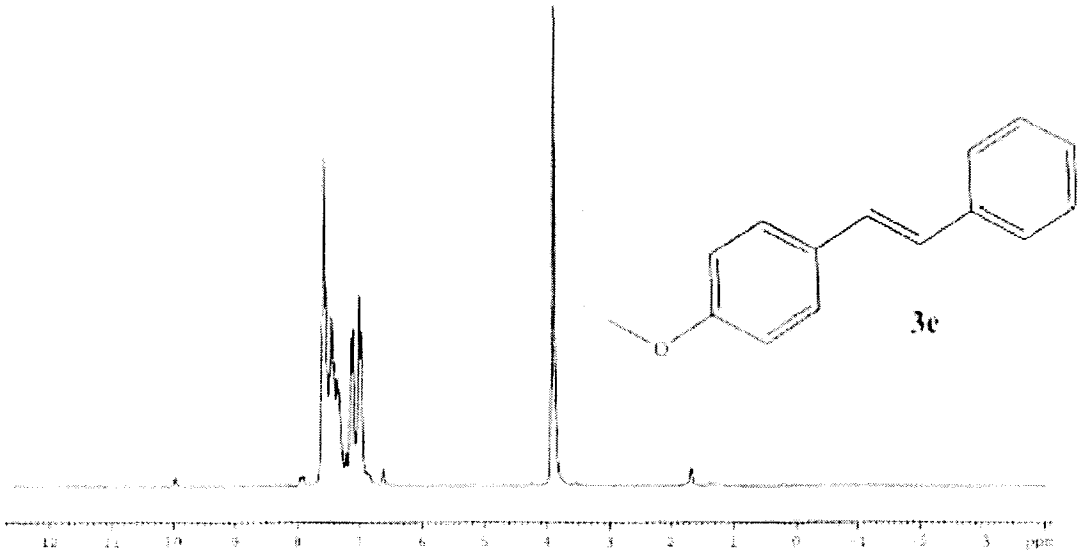

3b

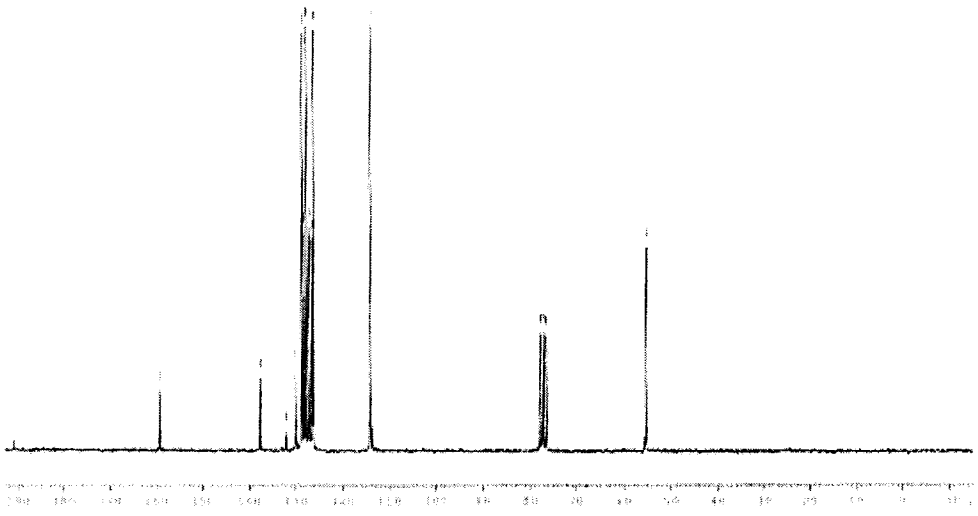

PPM
200
180
160
140
120
100
80
60
40
20
0

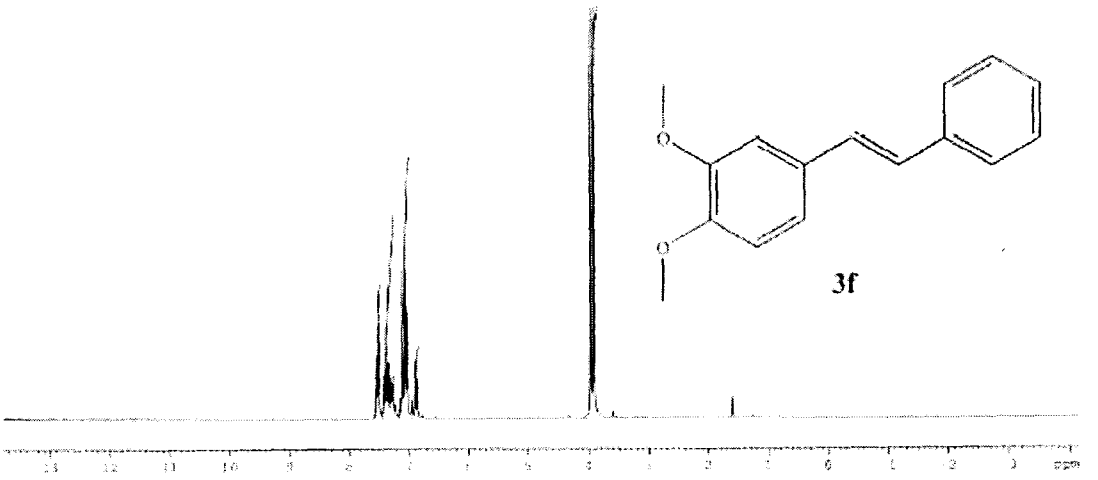



O_2N
3d

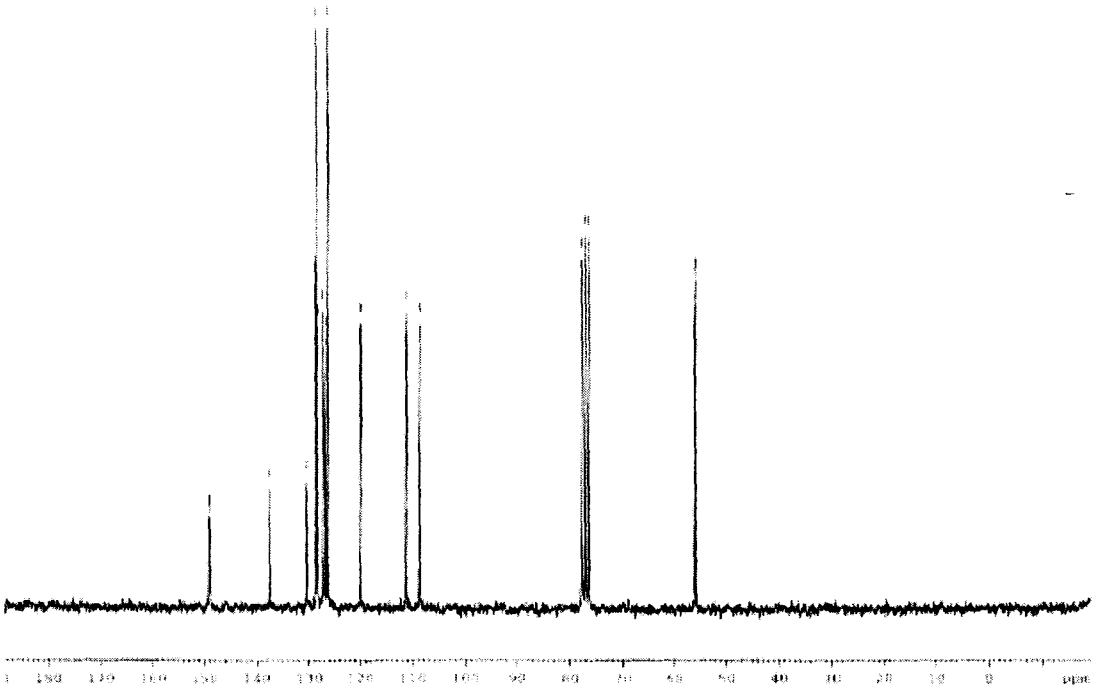


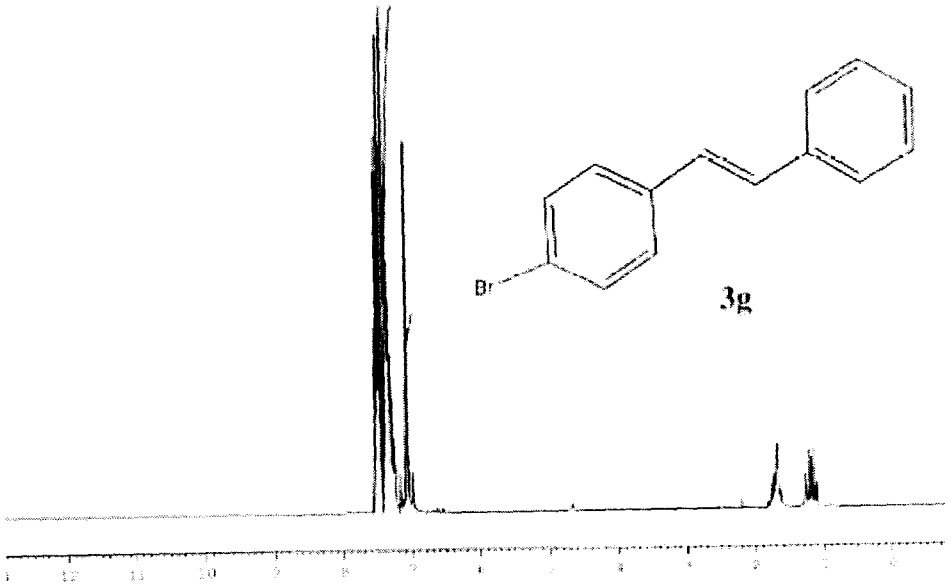

3e



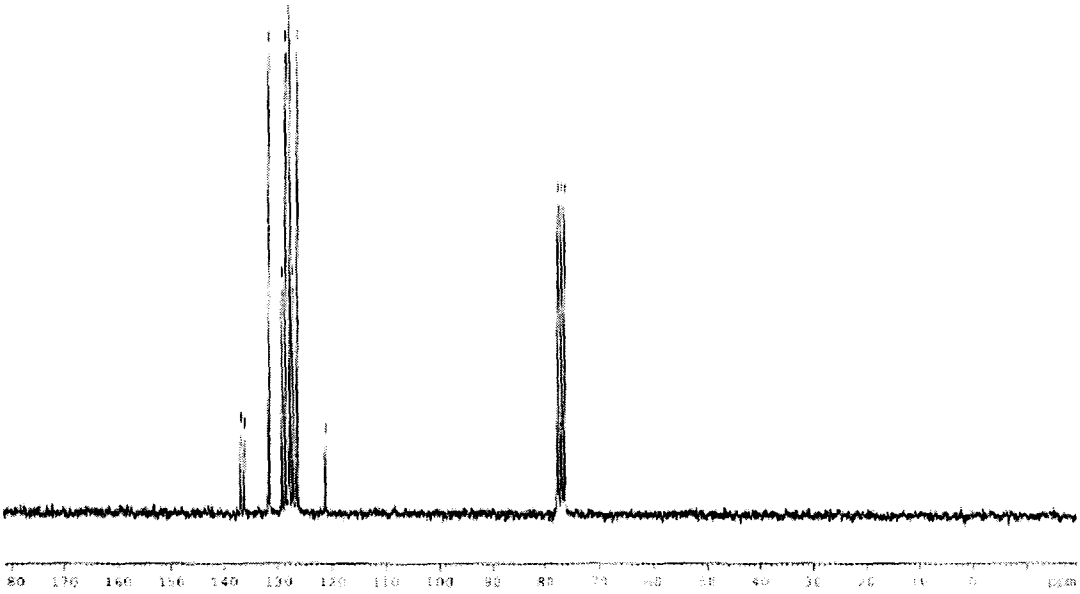


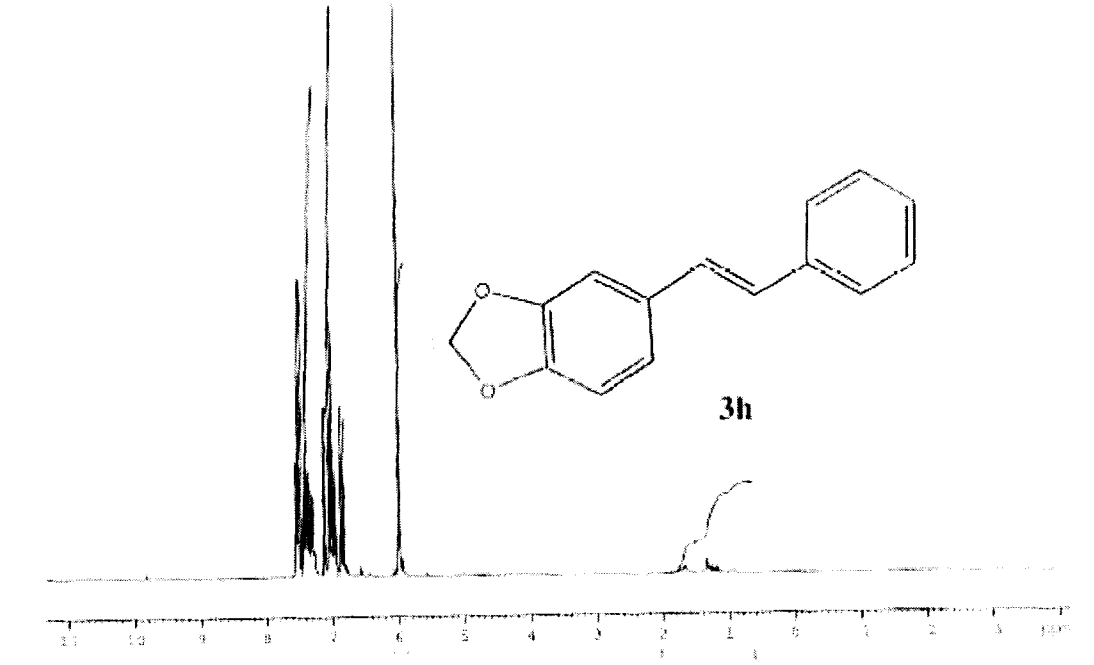
3f



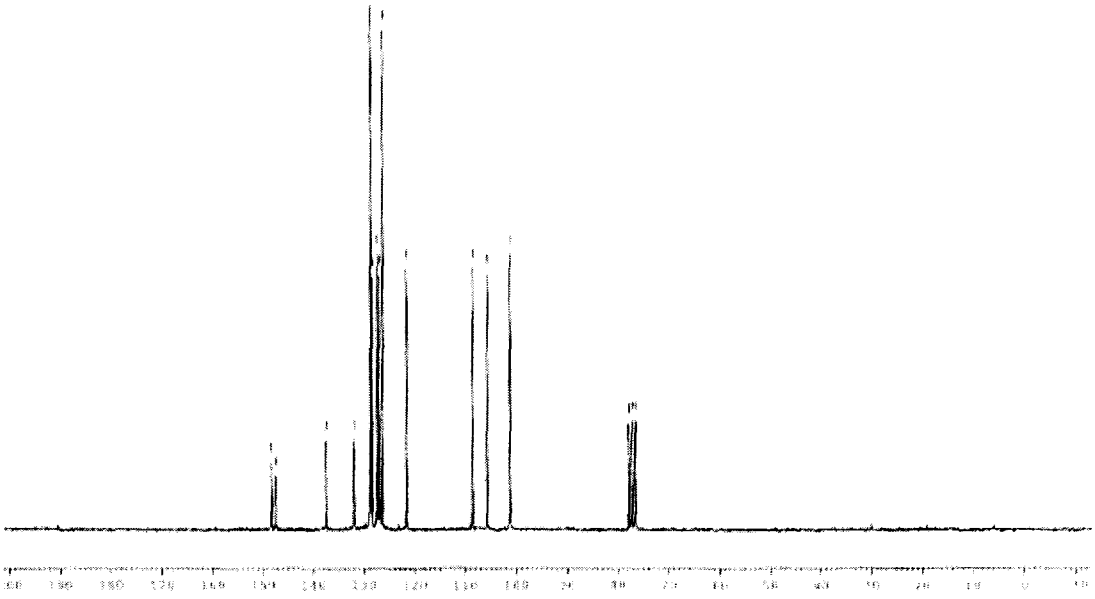


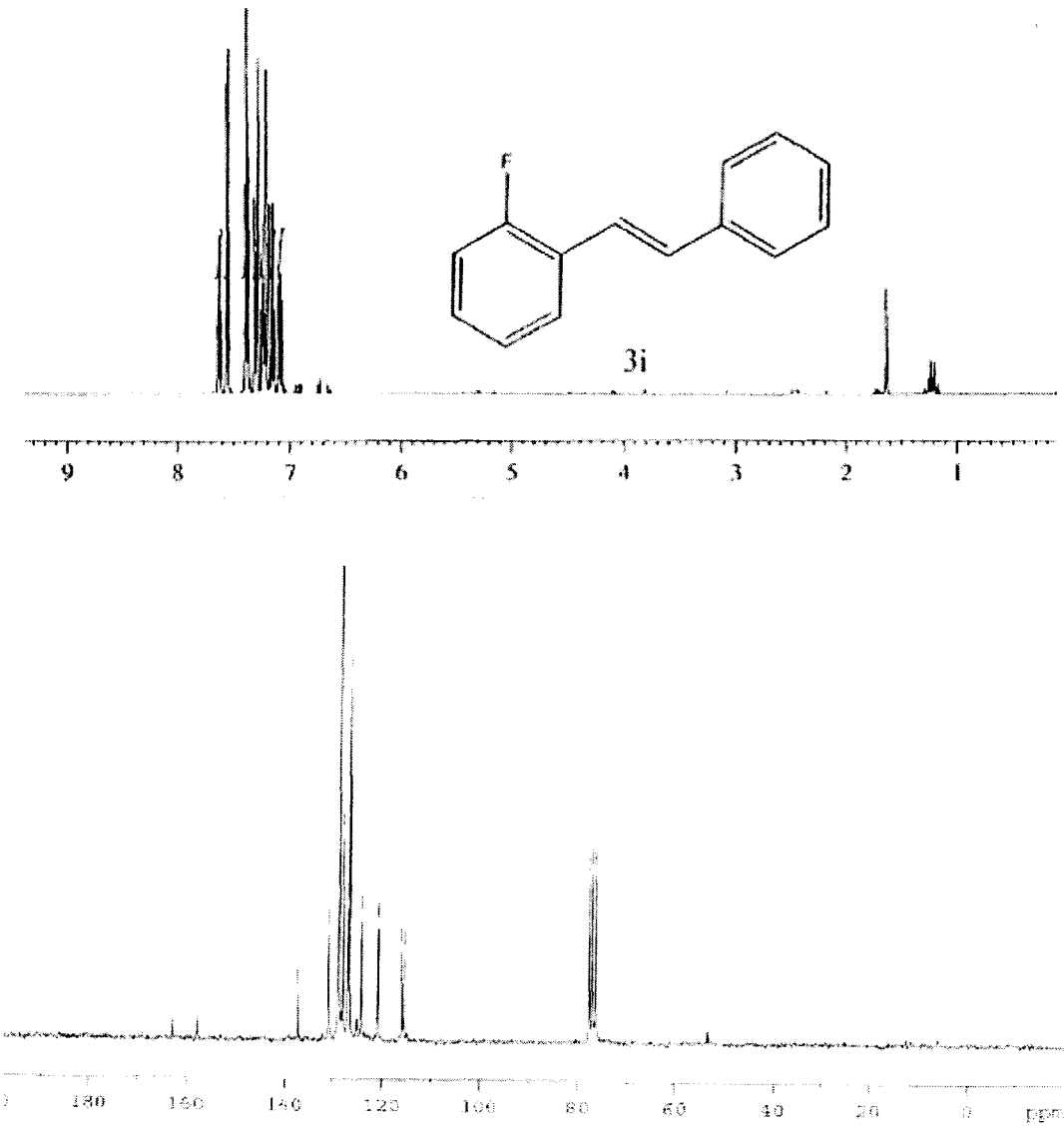
3g

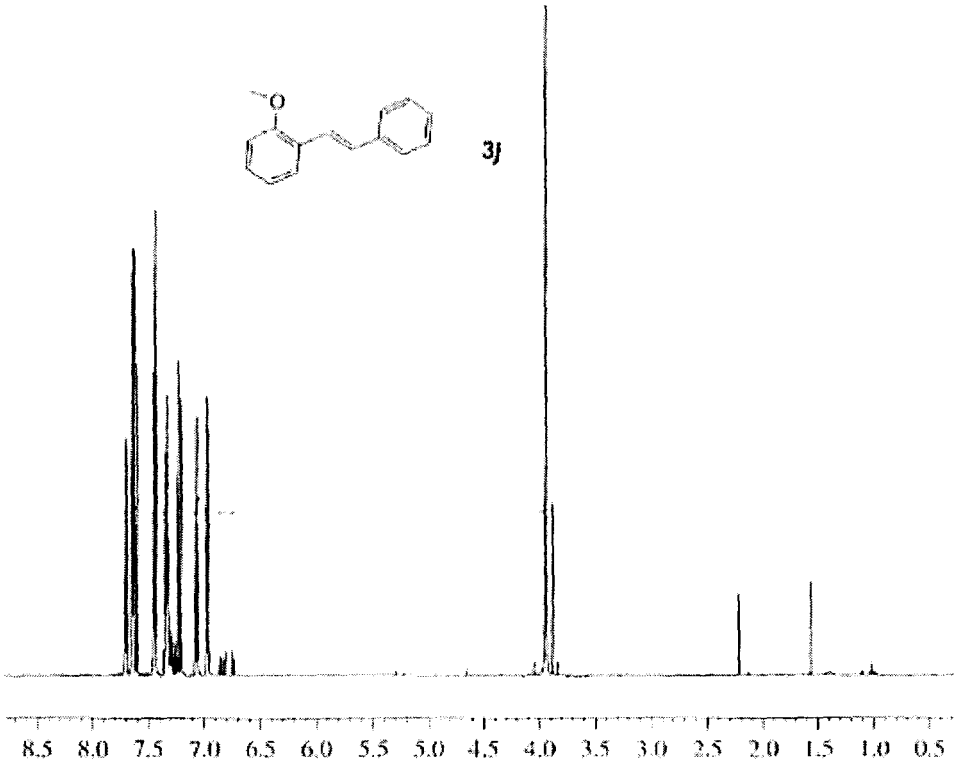


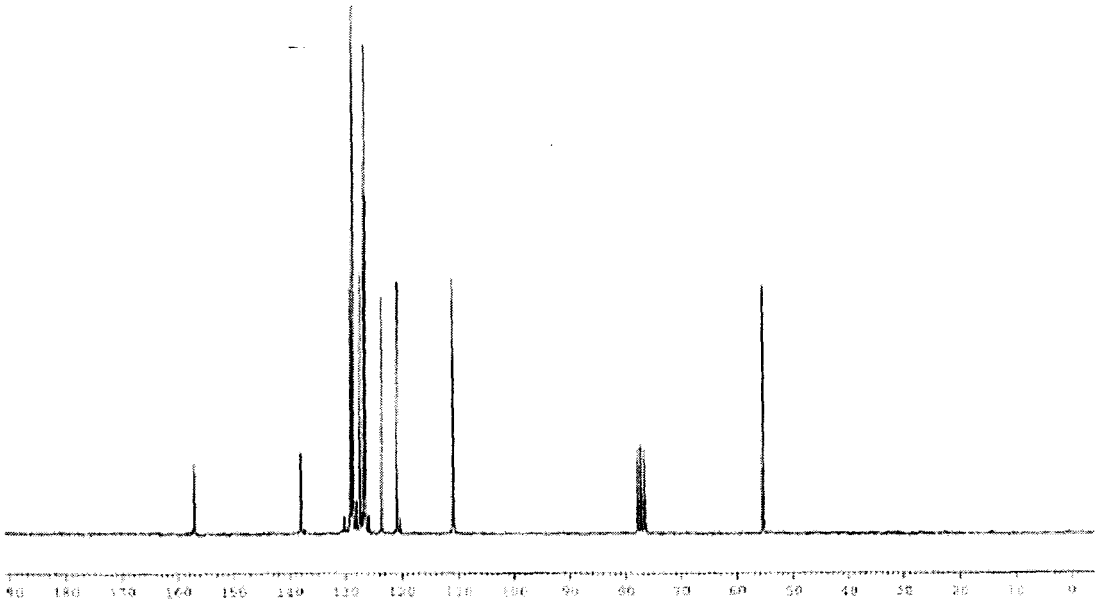


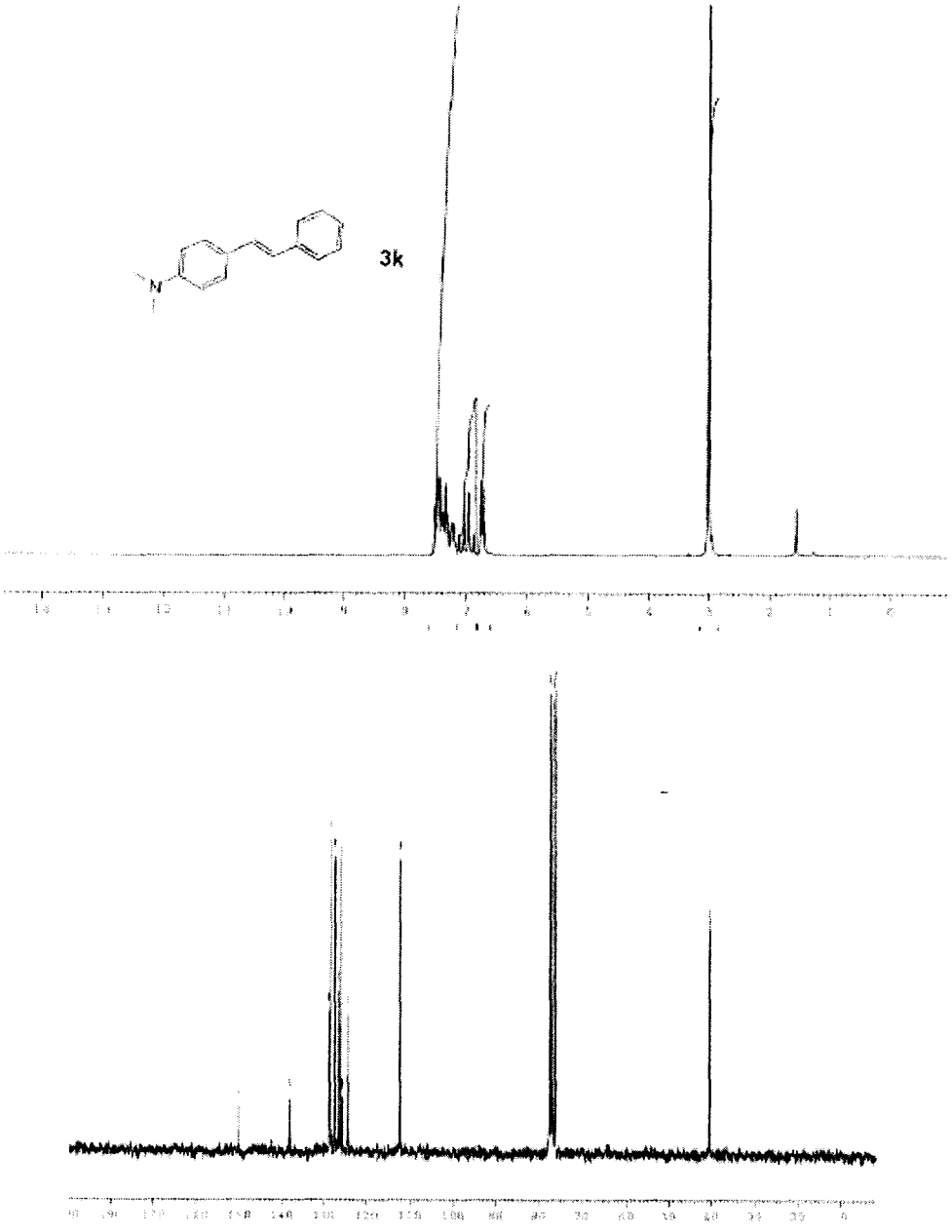
3h

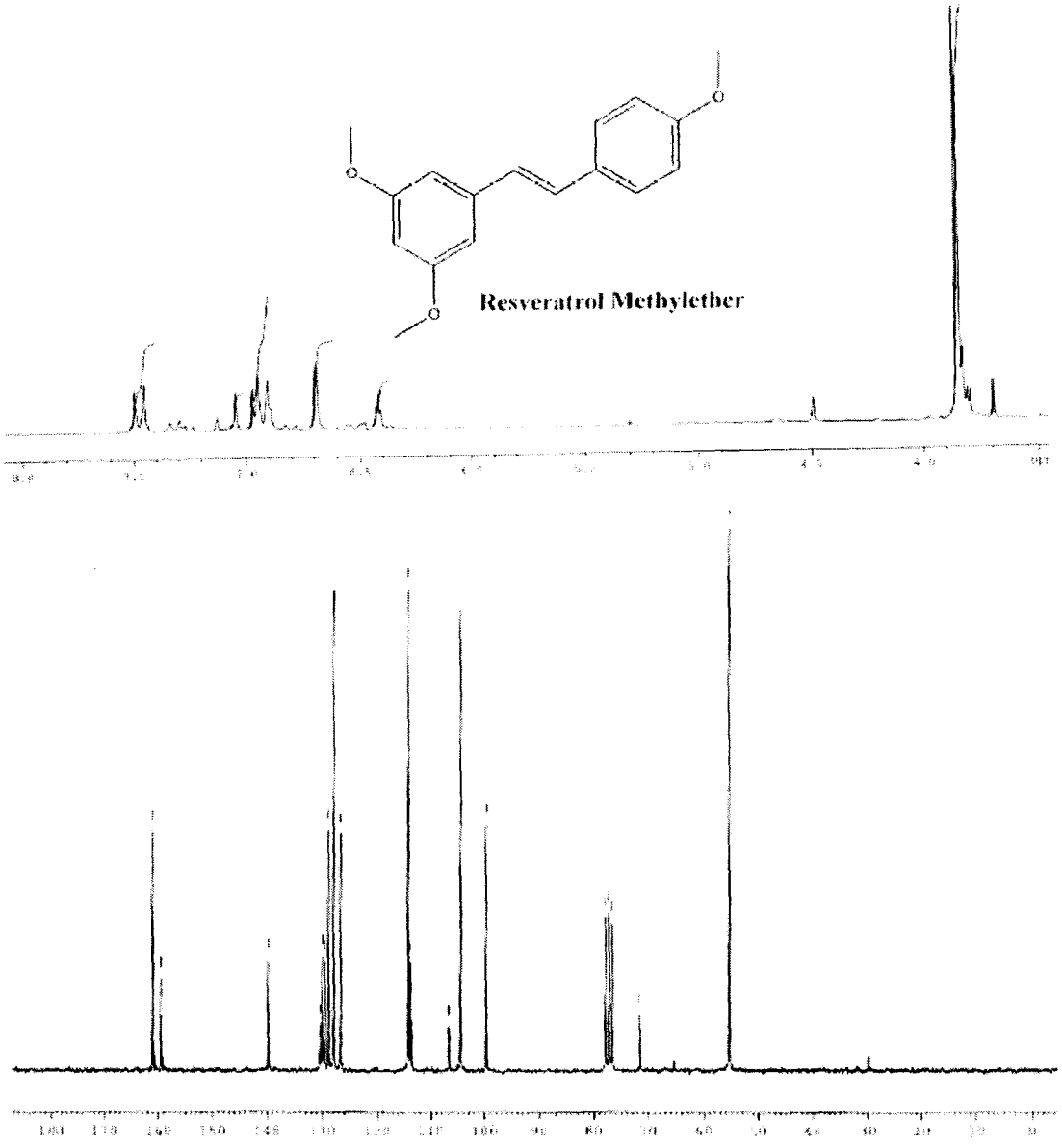


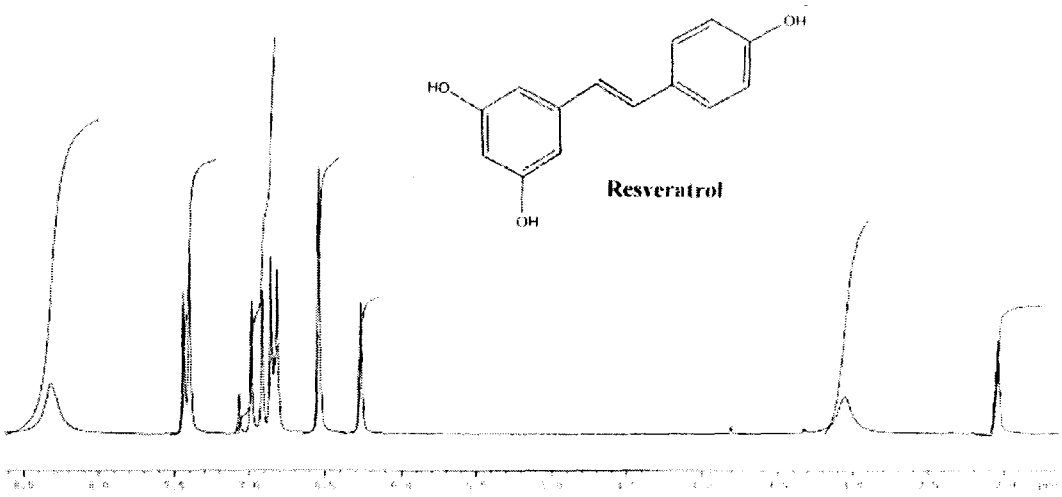

F
3i
9
8
7
6
5
4
3
2
1
180
160
140
120
100
80
60
40
20
0
ppm


O
3j
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

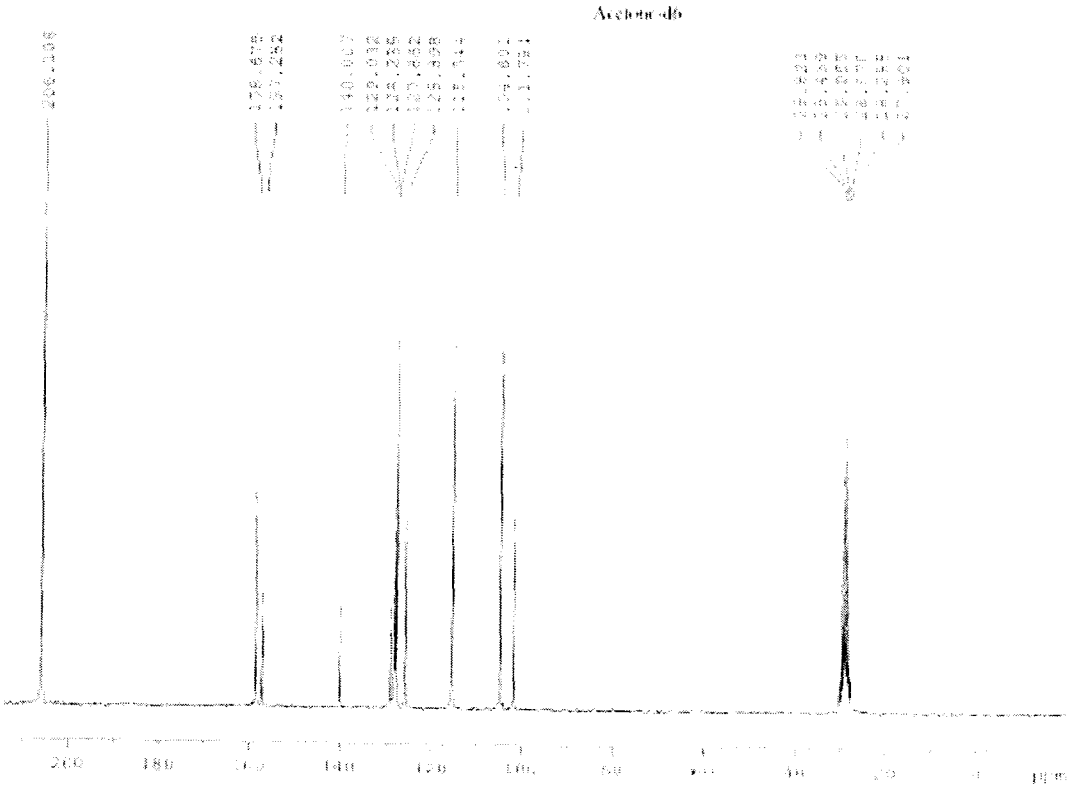


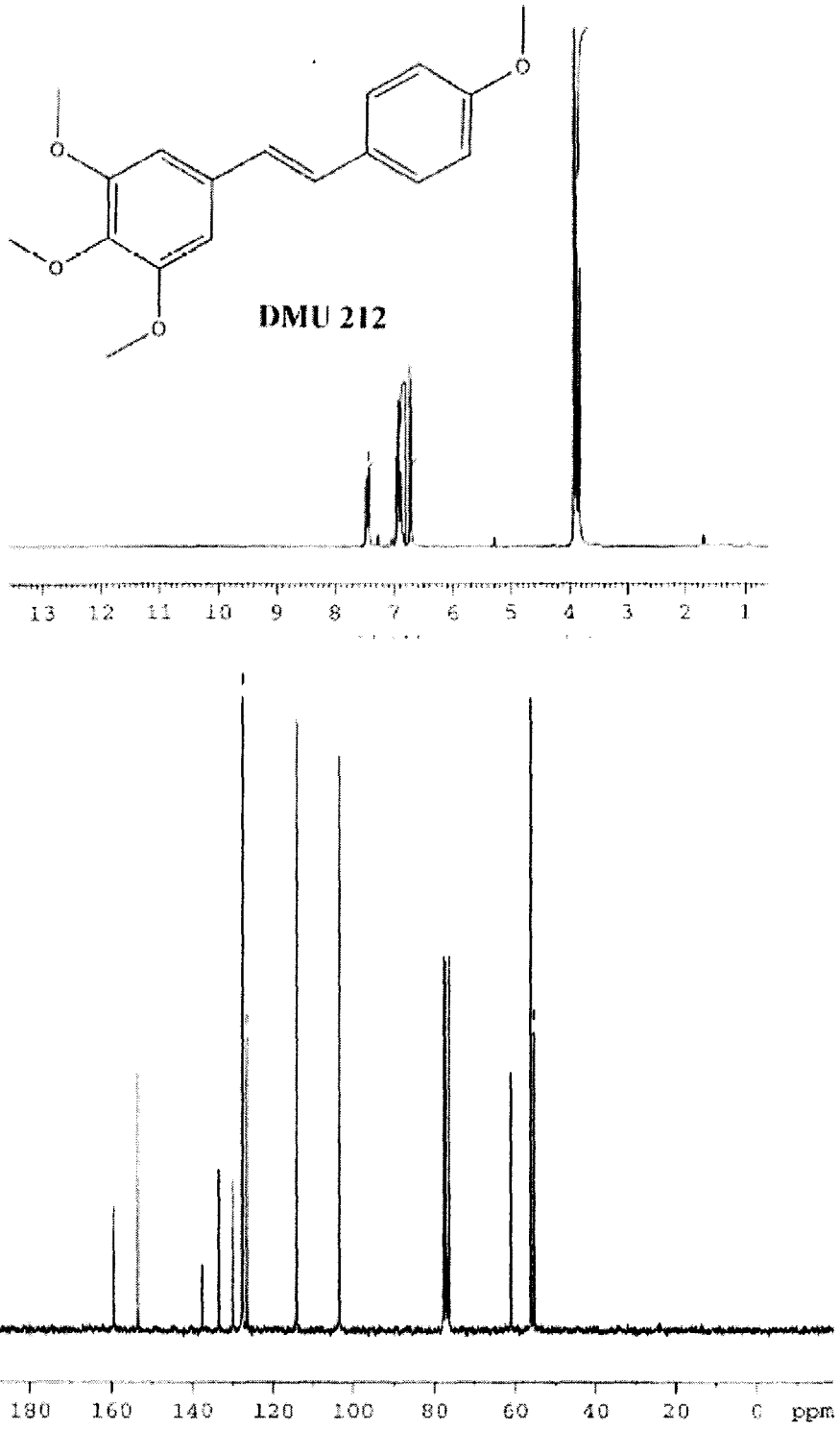

3k


Resveratrol Methylether



Resveratrol




DMU 212
13 12 11 10 9 8 7 6 5 4 3 2 1
180 160 140 120 100 80 60 40 20 0 ppm

Chapter VI

Aqueous Wittig Reactions of Semi-stabilized Ylides: A Straightforward Synthesis of 1,3-dienes and 1,3,5-trienes

Introduction:

The synthesis of functionalized 1,3-dienes and homologous polyenes is a central concern in synthetic organic chemistry. The 1,3-diene sub-unit is itself found in a wide range of bioactive materials including terpenoids, fatty acid derived lipids, pheromones and polyketides.[1] In addition, functionalized 1,3-dienes are of central importance as the 4π-component in Diels-Alder cycloaddition and other reactions, leading to a wide array of complex intermediates.[2] The Wittig olefination reaction of a triphenylallylidenyl ylide with a carbonyl compound is possibly the most general method available for preparing functionalized 1,3-dienes, Figure 1.[3a-c] While the use of triphenylphosphine derived ylides (R'= Ph) generally results in poor (*E*):(*Z*) stereoselection, subsequent methods advanced by Vedejs ,[3d] Tamura,[3c,f] Schlosser[3g] and others[3h] using mixed aryl/alkyl and alkyl-substituted phosphines were shown to provide higher levels of (*E*)-olefin stereoselectivity. Other recent related methods for the synthesis of conjugated alkenes include the use of ylides derived from arsonium salts,[3i] in addition to a variety of metal catalyzed cross-coupling processes.[3j]

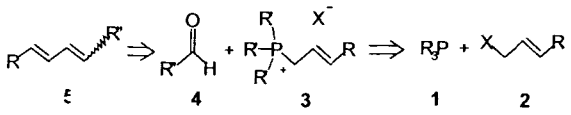


Figure 1. General Wittig route to 1,3-dienes **5**

We recently reported the first examples of the Wittig reaction involving tri*alkyl*phosphine derived semi-stabilized benzylidenyl ylides in water.[4] Water has been used previously as

the reaction media for the Wittig reaction of stabilized ylides[5] giving unsaturated esters. The reaction of triphenyl-substituted benzylidenyl ylides with aldehydes has also been reported in water,[6] providing stilbenes with poor configurational selectivity and requiring chromatographic purification to remove triphenylphosphine oxide. To our knowledge, the use of trialkyl allylidenyl ylides has not heretofore been performed in aqueous media. In our recent report,[4] triethylbenzyl phosphonium salts were converted chemoselectivity to the benzylidenyl phosphorane in water using simply sodium or lithium hydroxide as base. These ylides were shown to react with a range of aldehydes yielding stilbenes and 1-phenylalkenes in high yield. The major advantages of this process are the high (*E*)-olefin stereoselectivity and the easy separation of the water soluble triethylphosphine oxide from the organic product which generally precipitated from the aqueous solution. In this Letter we report the first examples of the aqueous Wittig reaction of trialkylallylphosphonium salt derived semi-stabilized ylides allowing for the succesful synthesis of a range of functionalized 1,3-dienes and 1,3,5-trienes.

Results & Discussion:

We first investigated the aqueous Wittig reaction of ylides derived from the three different trialkylallyl- phosphonium salts shown in Figure 2. These salts were pre-formed by reaction of the corresponding tertiary phosphine with allyl bromide. The salts were dissolved in 4.0 M aqueous NaOH (4 equivalents) and 3,4,5- trimethoxybenzaldehyde added. The reaction went to completion within one hour at 70 °C yielding the desired 1-phenyl-1,3-diene. Both the isolated chemical yield and the (*E*)-stereoselectivity of the resulting diene were shown to be highest for the triethylallyl-derived ylide.

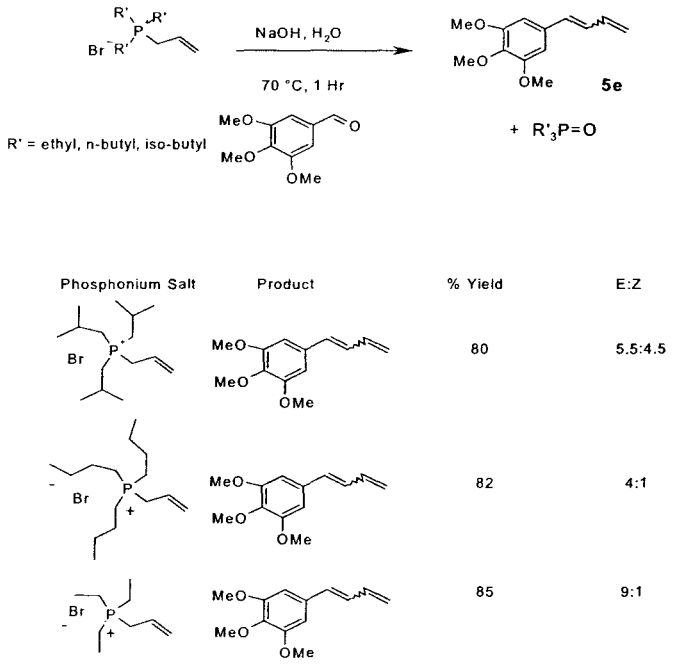


Figure 2 Phosphonium salt screening for *E* selectivity

The triethylallylphosphonium bromide was next screened in the aqueous Wittig reaction with a range of aromatic aldehydes, solely in aqueous sodium hydroxide under the conditions described above. The overall results of this investigation are summarized in Table 1. In many cases, the product diene oils-out or precipitates from the aqueous media during the reaction or upon cooling. The dienes were partitioned between dichloromethane and water and ran through a short column of silica to effect isolation of the (*E*):(*Z*) mixture. In a few cases the individual stereoisomers were readily separable. The isolated yields of the 1,3-dienes were high in all cases investigated. The (*E*):(*Z*)-stereoseletivity of the aqueous Wittig reaction was also generally high, and in accord with earlier results conducted in THF using *t*-BuOK or *n*-BuLi as base.[3d,f] The reaction proved applicable to a wide range of hetero-substituted aromatic aldehydes, including *ortho*-substituted derivatives. The reactions of both 2-chloro and 2-fluoro benzaldehyde resulted in higher (*Z*)-stereoselectivity than initially anticipated.

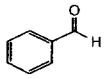
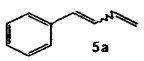
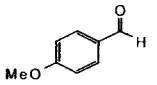
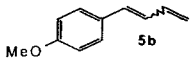
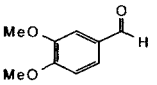
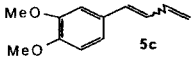
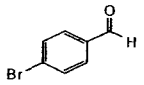
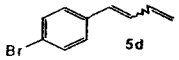
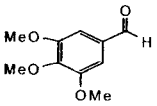
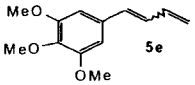
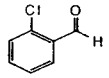
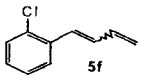
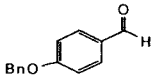
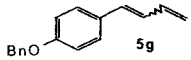
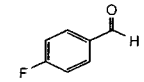
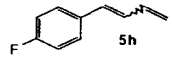
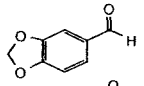
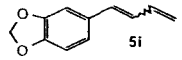
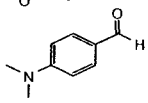
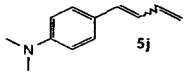
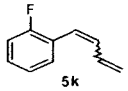
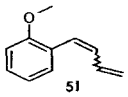
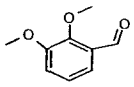
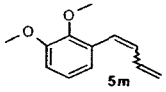
R-CHO	1,3-Diene	Yield	(*E*):(*Z*)
	 **5a**	80	4:1
	 **5b**	81	3:1
	 **5c**	85	8.5:1.5
	 **5d**	95	3 : 1
	 **5e**	85	9 : 1
	 **5f**	90	1.1 : 1
	 **5g**	92	4 : 1
	 **5h**	90	9.5 : 0.5
	 **5i**	85	4 : 1
	 **5j**	85	8.5 : 1.5
	 **5k**	85	7 : 3
	 **5l**	83	3.5 : 1
	 **5m**	87	4 : 1

Table 1. Synthesis of 1-phenyl-1,3-dienes from aromatic aldehydes using the aqueous Wittig reaction.

The increased (*Z*)-stereoselectivity and anamolous effects of 2-halo benzaldehyde derivatives has previously been reported.[7] The aqueous Wittig reaction of

triethylallylphosphonium bromide was next investigated with a series of α,β-unsaturated and aliphatic aldehydes, the results of which are summarized in Table 2. The unsaturated aldehydes allowed ready access to the corresponding 1,2,3-trienes from a variety of cores including monoterpenoid, aliphatic and aromatic cases and appears to be very general. Isolated yields were in the 80% range with good to high (*E*) stereoselectivity being observed.

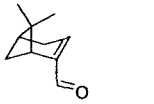
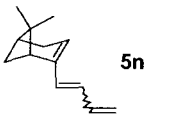
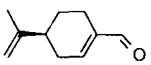
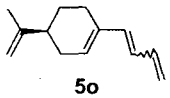
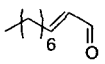
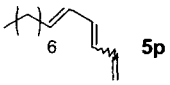
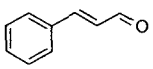
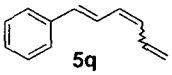
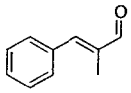
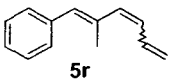
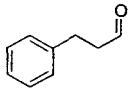
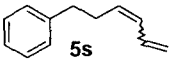
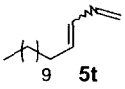
R-CHO	Polyene	Yield	(*E*):(*Z*)
	 **5n**	80	9:1
	 **5o**	78	9:1
	 **5p**	80	3:2
	 **5q**	80	7:3
	 **5r**	79	4:1
	 **5s**	73	4:1
	 **5t**	70	4:1

Table 2. Synthesis of polyenes from trialkylallylidenyl ylides with unsaturated and enolizable aliphatic aldehydes.

Most interestingly, the enolizable aliphatic aldehydes dihydrocinnamaldehyde and dodecanal were also observed to react selectively with the allyl ylide generated under these aqueous basic conditions. Only traces of polar impurities were observed and the

corresponding 1,3-dienes were isolated in 73% and 70% yield respectively. This chemoselectivity favouring olefination over potential homo-aldol or Cannizaro-type products under conditions that are classically known to effect these reactions is startling. We have postulated that this chemoselectivity is due to the formation of phosphonium salt stablilized micelles that effectively partitions the organic materials from the aqueous basic environment during the reaction. Ylide formation occurs at the interface and delivery of the neutral ylide and olefination takes place in the organic interior of the micelle.

Conclusion:

In conclusion, the Wittig reaction of trialkylallyl phosphonium salts has been demonstrated for the first time in water using sodium hydroxide as base. Ylide formation occurs exclusively through deprotonation at the allylic position. The resulting ylides were shown to react with a series of aromatic, unsaturated and enolizable aliphatic aldehydes yielding a structurally diverse range of useful 1,3-dienes and 1,3,5-trienes. The reaction is observed to be very chemoselective for olefination under conditions where competing homo-aldol or Cannizaro disproportionation reactions might be anticipated. Further studies on the mechanism of this simple, chemoselective polyene synthesis and applications on the reactions of other trialklylphosphine derived semi-stabilized ylides in aqueous media is under investigation.

References:

1. (a) Han, A. H.; Kim, M. S.; Jeong, Y. H.; Lee, S. K.; Seo, E. K. *Chem. Pharm. Bull.* **2005**, *53*, 1466-1468. (b) Pereira, A. R.; Cabezas, J. A. *J. Org. Chem.* **2005**, *70*, 2594-2597. (c) Moreira, J. A.; McElfresh, J. S.; Millar, J. G. *J. Chem. Ecol.*

2006, *32*, 169-194. (d) de Figueiredo, R. M.; Berner, R.; Julis, J.; Liu, T.; Turp, D.; Christmann, M. *J. Org. Chem.* **2007**, *72*, 640-642.

2. (a) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2007**, *72*, 4293-4305. (b) Kobayashi, S.; Jorgensen, K. A. in *Cycloaddition Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2002. (c) Rappaport, Z. in *The Chemistry of Dienes and Polyenes*, Vol. 1, Wiley, New York, 1997.
3. (a) Takeda, T. in *Modern Carbonyl Olefination*, Wiley-VCH, Weinheim, 2004. (b) Vedejs, E.; Peterson, M.J. *Top. Stereochem.* **1994**, 21, 1-157. (c) Maryanoff B. E.; A.B. Reitz, A. B. *Chem Rev.* **1989**, *89*, 863-927. (d) Vedejs, E.; Fan, H. W. *J. Org. Chem.* **1984**, *49*, 210-212. (e) Tamura, R.; Kato, M.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1987**, *52*, 4121-4124. (f) Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1988**, *53*, 2723-2728. (g) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821-5823. (h) Blade-Font, A.; Vander Werf, C. A.; McEwen, W. E. *J. Am. Chem. Soc.* **1960**, *82*, 2396-2397. (i) Habrant, D.; Stengel, B.; Meunier, S.; Miokowski, C. *Chem. Eur. J.* **2007**, *13*, 5433-5440. (j) Cahiez, G.; Habiak, V.; Gager, O. *Org. Lett.* **2008**, *10*, 2389-2392.
4. McNulty, J.; Das, P. *Eur. J. Org. Chem.*, in press.
5. (a) Dambacher, J.; Zhao, W.; El-Batta, A.; Anness, R.; Jiang, C.; Bergdahl, M. *Tetrahedron Lett.* **2005**, *46*, 4473-4477. (b) Wu, J.; Zhang, D.; Wei, S. *Synth. Commun.* **2005**, *35*, 1213-1222. (c) F. Orsini, F.; Sello, G.; Fumagalli, T. *Synlett* **2006**, 1717-1718. (d) Thiemann, T.; Watanabe, M.; Tanaka, Y.; Mataka, S. *New J. Chem.* **2006**, *30*, 359-369. (e) El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. *J. Org. Chem.* **2007**, *72*, 5244-5259. (f) Molander,

G. A.; Oliveira, R. A. *Terahedron Lett.* **2008**, **49**, 1266-126. (g) Tiwari, S.; Kumar, A. *Chem.Comm.* **2008**, 4445-4447.

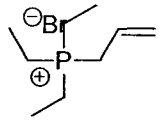
6. (a) Hwang, J. J.; Lin, R. L. Shieh, R. L.; Jwo, J. J. *J. Mol. Cat. A, Chemical,* **1999**, *142*, 125-139. (b) Wu, J.; Li, D.; Zhang, D. *Synth. Commun.* **2005**, *35*, 2543-2551. (c) Busafi, S. A.; Rawahi, W. A. *Ind. J. Chem.* **2007**, *46B*, 370-374.
7. Dunne, E. C.; Coyne, E. J.; Crowley, P. B.; Gilheany, D. G. *Tetrahedron Lett.* **2002**, *43*, 2449-2453.

Experimental:

General Information:

Phosphonium salts were prepared under argon in oven-dried glassware; Wittig reactions were carried out in distilled water under open air conditions. All fine chemicals were obtained from Aldrich except triethylphosphine, tributylphosphine and triisobutylphosphine, which were obtained from Cytec industries. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV and HRMS (EI) were performed with a Micromass Q-Tof Ultima spectrometer. ^{1}H, ^{13}C and ^{31}P spectra were recorded on a Bruker 200, AV 600 and AV 700 spectrometer in $CDCl_3$ with TMS as internal standard. Chemical shifts (δ) are reported in ppm downfield of TMS and coupling constants (J) are expressed in Hz. Signal assignments were accomplished *via* analysis of HMBC, HMQC, COSY, NOSEY experiments where necessary. The (*E*) to (*Z*) ratios were determined from the relative integration of the ^{1}H spectra of the olefinic protons.

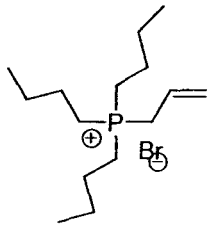
Allyl-triethylphosphonium-bromide:



Into a flame dried flask was added triethylphosphine (1 mL, 6.80 mmol) in dry dichloromethane (6.8 mL) under argon at 0 °C. To this was added allyl-bromide (589 µL, 6.80 mmol) via syringe. The solution was warmed to room temperature and stirred for 50 min. The solvent was evaporated under vacuum to yield the title compound in 99% yield (2.2 g) as white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.17 (dt, J_{PH} = 19.3 Hz, J_{HH} = 7.3 Hz, 9H), 2.38 (m, 6H), 3.36 (dd, J_{PH} = 16.8 Hz, J_{HH} = 8.4 Hz, 2H), 5.2-5.8 (m, 3H); ^{13}C-

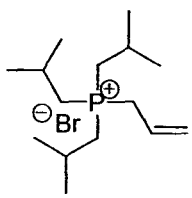
NMR (50 MHz, $CDCl_3$): δ 6.0, 12.1 (d, J_{PC} = 48.2 Hz), 24.0 (d, J_{PC} = 46.6 Hz), 123.9 (d, J_{PC} = 12.9 Hz), 124.4 (d, J_{PC} = 11.6 Hz); ^{31}P-NMR (80 MHz, $CDCl_3$): 36.8; HRES MS $(M)^+$ calcd. for $C_9H_{20}P$: 159.1306, found 159.1303.

Allyl-tri-n-butylphosphonium-bromide:



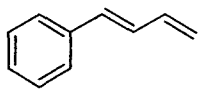
In a flame dried flask was added tri-n-butylphosphine (1 mL, 4 mmol) in dry dichloromethane (4 mL) under argon and cooled at 0 °C. To this was added allyl-bromide (346 μL, 4 mmol) via syringe. The solution was then warmed to room temperature and stirred for 50 min. The solvent was evaporated under vacuum to yield the title compound in 99% yield (1.3 g) as white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.85 (m, 9H), 1.42 (m, 12H), 2.35 (m, 6H), 3.42 (dd, J_{PH} = 15.6 Hz, J_{HH} = 7.2 Hz, 2H), 5.21-5.82 (m, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.4, 18.8 (d, J_{PC} = 46.7 Hz), 23.7 (d, J_{PC} = 4.5 Hz), 23.9 (d, J_{PC} = 20.7 Hz), 25.2 (d, J_{PC} = 46.7 Hz), 124.1 (d, J_{PC} = 9.8 Hz), 124.4 (d, J_{PC} = 11.7 Hz); ^{31}P-NMR (80 MHz, $CDCl_3$): 31.3; HRES MS $(M)^+$ calcd. for $C_{15}H_{32}P$: 243.2243, found 243.2242.

Allyl-tri-iso-butylphosphonium-bromide:



In a flame dried flask was added tri-iso-butylphosphine (1 mL, 4 mmol) in dry dichloromethane under argon and cooled at 0 °C. Allyl-bromide (346 μL, 4 mmol) was then added via syringe, the solution warmed to room temperature and allowed to stir overnight. The solvent was evaporated under vacuum to yield the title compound in 98% yield (1.3 g) as a white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.93 (m, 18H), 2.05 (m, 3H), 2.27 (m, 6H), 3.41 (dd, J_{PH} = 15.1 Hz, J_{HH} = 6.7 Hz, 2H), 5.23-5.79 (m, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 23.6 (d, J_{PC} = 4.1 Hz), 24.8 (d, J_{PC} = 8.5 Hz), 27.1 (d, J_{PC} = 45.3 Hz), 28.8 (d, J_{PC} = 43.2 Hz), 124.2 (d, J_{PC} = 9.5 Hz), 124.9 (d, J_{PC} = 11.9 Hz); ^{31}P-NMR (80 MHz, $CDCl_3$): 29.5; HRES MS $(M)^+$ calcd. for $C_{15}H_{32}P$: 243.2243, found 243.2236.

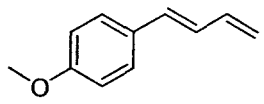
(*1E*)-1-Phenyl-1,3-butadiene[1] 5a:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min benzaldehyde (102 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (hexane) to yield the title compound **5a,** 105.5

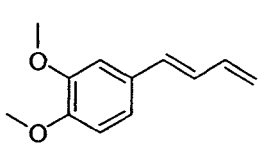
mg, (81%) as brown oil. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.27 (d, J_{HH} = 10.4 Hz, 1H), 5.42 (d, J_{HH} = 16.4 Hz, 1H), 6.62 (ddd, J_{HH} = 16.6 Hz, 10.3 Hz, 10.1 Hz, 1H), 6.67 (d, J_{HH} = 15.8 Hz, 1H), 6.91 (dd, J_{HH} = 16.0 Hz, 10.7 Hz, 1H), 7.34 (m, 1H), 7.42 (m, 4H).

(*1E*)-1-(4'methoxy)phenyl-1,3-butadiene[2] 5b:



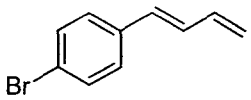
Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 4-methoxybenzaldehyde (122 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1.5 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (7.5% ethyl acetate in hexane) to yield the title compound **5b,** 128 mg, (80%) as yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.80 (s, 3H); 5.10 (d, J_{HH} = 9.9 Hz; 1H), 5.25 (d, J_{HH} = 16.1 Hz; 1H), 6.50 (d, J_{HH} = 15.0 Hz; 1H), 6.38 (m, 1H), 6.67 (dd, J_{HH} = 15.0 Hz, 10.7 Hz, 1H), 6.83 (d, J_{HH} = 8.2 Hz, 2H), 7.32 (d, J_{HH} = 8.4 Hz, 2H).

(*1E*)-1-(3',4'dimethoxy)phenyl-1,3-butadiene[3] 5c:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 3'4-dimethoxybenzaldehyde (166.2 mg, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (15% ethyl acetate in hexane) to yield the title compound **5c,** 162 mg, (85%) as yellow semisolid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.87 (s, 3H), 5.10 (d, J_{HH} = 10.8 Hz, 1H), 5.27 (d, J_{HH} = 17.2 Hz, 1H), 6.45 (m, 2H), 6.64 (dd, J_{HH} = 15.7 Hz, 10.5 Hz, 1H), 6.76 (d, J_{HH} = 8.3 Hz, 1H), 6.68 (dd, J_{HH} = 11.3 and 1.8 Hz, 1H), 6.92 (d, J_{HH} = 1.8 Hz, 1H).

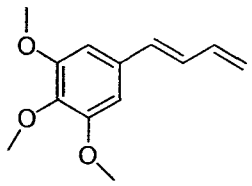
(*1E*)-1-(4' bromo)phenyl-1,3-butadiene 5d:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 4-bromobenzaldehyde (185 mg, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask

was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (10% ethyl acetate in hexane) to yield the title compound **5d,** 199 mg, (95%) as yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.23 (d, J_{HH} = 9.8 Hz, 1H), 5.36 (d, J_{HH} = 16.8 Hz, 1H), 6.48 (m, 2H), 6.76 (dd, J_{HH} = 9.8 Hz, 5.6 Hz, 1H), 7.25 (d, J_{HH} = 8.4 Hz, 2H), 7.44 (d, J_{HH} = 8.4 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 118.5, 121.0, 128.0, 130.4, 131.7, 131.8, 136.1, 137.0; HRCI MS $(M)^+$ calcd. for $C_{10}H_9Br$: 207.9888, found: 207.9892.

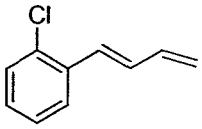
(*1E*)-1-(3'4'5' trimethoxy)phenyl-1,3-butadiene 5e:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 3'4'5-trimethoxybenzaldehyde (196.2 mg, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (35% ethyl acetate in hexane) to yield the title compound **5e,** 186 mg, (85%) as yellow semisolid. ^{1}H-NMR (600 MHz,

$CDCl_3$): δ 3.83 (s, 3H), 3.85 (s, 6H), 5.14 d, J_{HH} = 10.8 Hz, 1H), 5.31 (d, J_{HH} = 17.4 Hz, 1H), 6.47 (m, 2H), 6.61 (s, 2H), 6.68 (dd, J_{HH} = 10.2 Hz, 16.2 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 56.0, 60.9, 103.4, 117.5, 129.1, 130.5, 132.8, 133.1, 137.0, 153.3; HRCI MS $(M)^+$ calcd. for $C_{13}H_{16}O_3$: 220.1099, found: 220.1104.

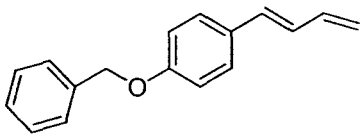
(*1E*)-1-(2' chloro)phenyl-1,3-butadiene 5f:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 2-chlorobenzaldehyde (113 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (10% ethyl acetate in hexane) to yield the title compound **5f,** 77.5 mg, (47.1%) as yellow oil. Yield of the *Z* isomer was 70.5 mg, (42.9%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.25 (d, J_{HH} = 10.2 Hz, 1H), 5.40 (d, J_{HH} = 16.2 Hz, 1H), 6.58 (m, 1H), 6.77 (dd, J_{HH} = 10.2 Hz, 15.6 Hz, 1H), 6.98 (d, J_{HH} = 15.6 Hz, 1H), 7.24 (m, 2H), 7.38 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 118.9, 126.2, 126.3,

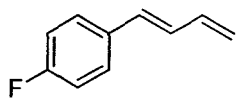
126.8, 128.7, 129.9,. 130.6, 132.1, 133.9, 137.2; HRCI MS $(M)^+$ calcd. for $C_{10}H_9Cl$: 164.0393, found: 164.0396.

(*1E*)-1-(4' benzyloxy)phenyl-1,3-butadiene 5g:



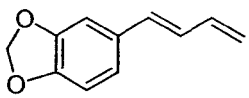
Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 4-benzyloxybenzaldehyde (212.3 mg, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (10% ethyl acetate in hexane) to yield the title compound **5g,** 217 mg, (92%) as yellow solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.1 (s, 2H), 5.20 (d, J_{HH} = 10.5 Hz, 1H), 5.36 (d, J_{HH} = 17.5 Hz, 1H), 6.57 (m, 2H), 6.74 (dd, J_{HH} = 10.5 Hz, 15.4 Hz, 1H), 7.01 (d, J_{HH} = 9.1 Hz, 2H), 7.38 (m, 5H), 7.49 (d, J_{HH} = 9.1 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 70.2, 115.2, 116.7, 127.6, 127.8, 127.9, 128.5, 128.8, 129.6, 130.3, 130.4, 158.6; HRCI MS $(M)^+$ calcd. for $C_{17}H_{16}O$: 236.1201, found: 236.1199.

(*1E*)-1-(4'fluoro)phenyl-1,3-butadiene[4] 5h:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 4-fluorobenzaldehyde (108 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (hexane) to yield the title compound **5h,** 133 mg, (90%) as colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.17 (d, J_{HH} = 10.1 Hz, 1H), 5.34 (d, J_{HH} = 16.8 Hz, 1H), 6.49 (ddd, J_{HH} = 16.7 Hz, 10.5 Hz, 10.1 Hz, 1H), 6.53 (d, J_{HH} = 15.6 Hz, 1H), 6.70 (dd, J_{HH} = 15.6 Hz, 10.5 Hz, 1H), 7.01 (dd, J_{HH} = 8.6 Hz, 8.4 Hz, 2H), 7.37 (dd, J_{HH} = 8.5 Hz, 5.5 Hz, 2H).

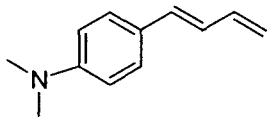
(*1E*)-1-(3'4 methelenedioxy)phenyl-1,3-butadiene 5i:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min piperonal (150.1 mg, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at

70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (20% ethyl acetate in hexane) to yield the title compound **5i,** 148 mg, (90%) as yellow solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.19 (d, J_{HH} = 11.4 Hz, 1H), 5.34 (d, J_{HH} = 17.5 Hz, 1H), 6.52 (m, 2H), 5.95 (s, 2H), 7.0 (s, 1H), 6.67 (dd, J_{HH} = 10.2 Hz, 14.4 Hz, 1H), 6.79 (d, J_{HH} = 7.8 Hz, 1H), 6.85 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 101.3, 105.5, 108.4, 116.9, 121.4, 128.0, 129.8, 132.6, 137.2, 147.3, 148.1; HRCI MS $(M)^+$ calcd. for $C_{11}H_{10}O_2$: 174.0681, found: 174.0678.

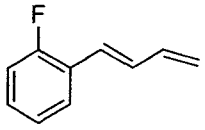
(*1E*)-1-(4' N'N-dimethylamino)phenyl-1,3-butadiene 5j:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 4-dimethylaminobenzaldehyde (149.2 mg, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (20% ethyl

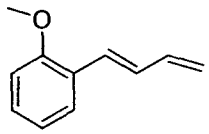
acetate in hexane) to yield the title compound **5j,** 147.2 mg, (85%) as orange solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 2.98 (s, 6H), 5.06 (d, J_{HH} = 10.5 Hz, 1H), 5.24 (d, J_{HH} = 17.5 Hz, 1H), 6.5 (m, 2H), 6.63 (m, 1H), 6.69 (d, J_{HH} = 7.2 Hz, 2H), 7.32 (d, J_{HH} = 7.2 Hz, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 40.7, 112.4, 115.0, 125.1, 127.5, 131.1, 133.3, 137.8, 150.1; HRCI MS $(M)^{+}$ calcd. for $C_{12}H_{15}N$: 173.1204, found: 173.1198.

(*1E*)-1-(2'fluoro)phenyl-1,3-butadiene[2] 5k:



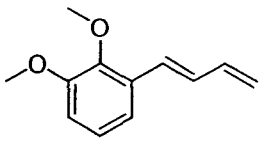
Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 2-fluorobenzaldehyde (105 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (hexane) to yield the title compound **5k,** 125.9 mg, (85%) as yellow semisolid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.19 (d, J_{HH} = 10.2 Hz, 1H), 5.35 (d, J_{HH} = 17.0 Hz, 1H), 6.50 (ddd, J_{HH} =17.0 Hz, 10.3 Hz, 10.3 Hz, 1H), 6.71 (d, J_{HH} = 15.8 Hz, 1H), 6.85 (dd, J_{HH} = 15.7 Hz, 0.4 Hz, 1H), 7.01 (m, 1H), 7.10 (ddd, J_{HH} = 7.3 Hz, 7.3 Hz, 0.9 Hz, 1H), 7.19 (m, 1H), 7.46 (ddd, J_{HH} = 9.5 Hz, 9.5 Hz, 1.8 Hz, 1H).

(*1E*)-1-(2'methoxy)phenyl-1,3-butadiene[7] 5l:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 2-methoxybenzaldehyde (120.7 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (10% ethyl acetate in hexane) to yield the title compound **5l,** 132.9 mg, (83%) as yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.85 (s, 3H), 5.14 (d, J_{HH} = 9.9 Hz, 1H), 5.31 (d, J_{HH} = 16.8 Hz, 1H), 6.52 (dt, J_{HH} = 16.9 Hz, 9.9 Hz, 1H), 6.85 (m, 4H), 7.22 (m, 1H), 7.47 (dd, J_{HH} =7.5 Hz, 1.8 Hz, 1H).

(*1E*)-1-(2'3' dimethoxy)phenyl-1,3-butadiene 5m:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 2'3-

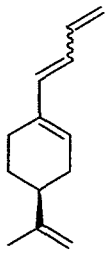
dimethoxybenzaldehyde (166.2 mg, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (15% ethyl acetate in hexane) to yield the title compound **5m,** 165.5 mg, (87%) as yellow semisolid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.83 (s, 3H), 3.87 (s, 3H), 5.19 (d, J_{HH} = 10.2 Hz, 1H), 5.35 (d, J_{HH} = 17.4 Hz, 1H), 6.57 (td, J_{HH} = 10.7 Hz, 17.4 Hz, 1H), 6.83 (m, 2H); 6.93 (d, J_{HH} = 15.6 Hz, 1H), 7.03 (d, J_{HH} = 7.8 Hz, 1H), 7.15 (d, J_{HH} = 7.8 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 55.8, 61.0, 111.4, 117.7, 117.8, 124.1, 127.1, 130.9, 131.6, 137.7, 146.8, 153.1; HRCI MS $(M)^+$ calcd. for: $C_{12}H_{14}O$: 190.0994, found: 190.0991.

2-((1'*E*)-buta-1',3'-dienyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene 5n:

Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min (1R)-(-)-myrtenal (152 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred

for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (hexane) to yield the title compound **5n,** 139 mg, (80%) as colorless oil. ^{1}H-NMR (700 MHz, $CDCl_3$): δ 0.80 (s, 3H), 1.13 (d, J_{HH} = 8.6 Hz, 1H), 1.34 (s, 3H), 2.12 (m, 1H), 2.37 (m, 3H), 2.59 (m, 1H), 5.03 (d, J_{HH} = 9.9 Hz, 1H), 5.17 (d, J_{HH} = 16.7 Hz, 1H), 5.60 (s, 1H), 6.14 (dd, J_{HH} = 15.5 Hz, 10.5 Hz, 1H), 6.25 (d, J_{HH} = 15.6 Hz, 1H), 6.4 (ddd, J_{HH} =16.9 Hz, 10.3 Hz, 10.3 Hz, 1H).

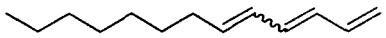
(1'*E*, 4*S*)-1-(buta-1',3'-dienyl)-4-(prop-1-en-2-yl)cyclohex-1-ene[6] 5o:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyltriethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min (S)-(-)-perillaldehyde (156 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (hexane) to yield the title compound **5o,** 136 mg, (78%) as yellow semisolid. ^{1}H-NMR (700 MHz, $CDCl_3$): δ 1.52

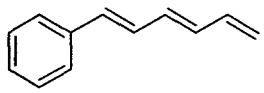
(m, 1H), 1.77 (s, 3H), 1.92 (m, 1H), 2.10 (m, 1H), 2.18 (m, 1H), 2.29 (m, 1H), 2.36 (m, 1H), 4.74 (d, J_{HH} = 10.5 Hz, 2H), 5.06 (d, J_{HH} = 10.5 Hz, 1H), 5.20 (d, J_{HH} = 17.5 Hz, 1H), 5.80 (m, 1H), 6.13 (dd, J_{HH} = 15.4 Hz, 10.5 Hz, 1H), 6.25 (d, J_{HH} = 15.4 Hz, 1H), 6.40 (m, 1H).

(*E,E,E*)trideca-1,3,5-triene 5p:



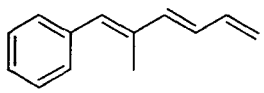
Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min trans-2-decenal (183μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (hexane) to yield the title compound **5p,** 85.8 mg, (48%) as yellow oil. Yield of the *Z* isomer was 57.2 mg, (32%). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.9 (M, 3H), 1.26 (m, 10H), 2.10 (m, 2H), 5.04 (d, J_{HH} = 8.4 Hz, 1H), 5.15 (d, J_{HH} = 14.4 Hz, 1H), 5.74 (m, 1H), 6.07 (m, 1H), 6.12 (m, 1H), 6.21 (m, 1H), 6.36 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.2, 22.7, 29.2, 32.9, 116.2, 130.0, 130.1, 133.7, 136.2, 137.2; HRCI MS $(M)^+$ calcd. for $C_{13}H_{22}$: 178.1722, found: 178.1724.

(1*E*, 3*E*)-1-Phenyl-1,3-5-hexatriene[8] 5q:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min trans-cinnamaldehyde (140 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (5% ethyl acetate in hexane) to yield the title compound **5q,** 156.2 mg, (80%) as yellow semisolid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.17 (d, J_{HH} = 9.6 Hz, 1H), 5.30 (d, J_{HH} = 17.4 Hz, 1H), 6.45 (m, 2H), 6.60 (d, J_{HH} = 15.6 Hz, 2H), 7.20-7.50 (m, 6H).

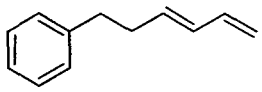
(1*E*, 3*E*)-1-Phenyl-2-methyl-1,3,5-hexatriene[9] 5r:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min trans-2-methylcinnamaldehyde (140 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was

left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (5% ethyl acetate in hexane) to yield the title compound **5r,** 134.5 mg, (79%) as yellow semisolid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 2.17 (s, 3H), 5.25 (d, J_{HH} = 10.8 Hz, 1H), 5.41 (d, J_{HH} = 16.3 Hz, 1H), 6.49 (dd, J_{HH} = 15.0 Hz, 10.2 Hz, 1H), 6.59 (m, 2H), 6.67 (s, 1H), 7.14-7.47 (m, 5H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.1, 117.1, 126.7, 128.4, 128.8, 129.4, 132.4, 134.1, 135.9, 137.7, 138.7.

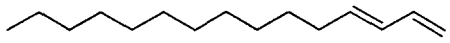
(3*E*)-6-phenylhexa-1,3-diene [9] 5s:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min hydrocinnamaldehyde (131.7 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (5% ethyl acetate in hexane) to yield the title compound **5s,** 115.5 mg, (73%) as yellow oil. ^{1}H-NMR (600

MHz, $CDCl_3$): δ 2.57 (m, 2H), 2.80 (t, J_{HH} = 9.6 Hz, 2H), 5.07 (dd, J_{HH} = 10.2 Hz, 1.7 Hz, 1H), 5.20 (dd, J_{HH} = 16.8 Hz, 1.7 Hz, 1H), 5.82 (dt, J_{HH} = 15.0 Hz, 6.7 Hz, 1H), 6.20 (dd, J_{HH} = 15.0 Hz, 11.6 Hz, 1H), 6.43 (ddd, J_{HH} = 16.8 Hz, 11.5 Hz, 10.2 Hz, 1H), 7.42-7.22 (m, 5H).

(3*E*)-pentadeca-1,3-diene[9] 5t:



Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The flask was stirred for 15 min at room temperature whereupon NaOH (160 mg, 4.0 mmol) was added slowly. After 2 mins dodecanal (222 μL, 1 mmol) was added slowly to the reaction flask. The flask was stirred vigorously at 70 °C for 1 hr. The oil bath was removed and the flask was left to attain room temperature. 5 mL water was added to the reaction mixture and the flask was stirred for 10 mins. The resulting mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified by silica gel column chromatography (hexane) to yield the title compound **5t,** 145.8 mg, (70%) as yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.90 (t, J_{HH} = 6.6 Hz, 3H), 1.10-1.50 (m, 18H), 2.30-2.03 (m, 2H), 4.95 (dd, J_{HH} = 10.1 Hz, 1.8 Hz, 1H), 5.07 (dd, J_{HH} = 17.2 Hz, 1.7 Hz, 1H), 5.71 (dt, J_{HH} = 15.2 Hz, 6.8 Hz, 1H), 6.06 (dd, J_{HH} = 15.0 Hz, 10.2 Hz, 1H), 6.32 (ddd, J_{HH} = 17.0 Hz, 10.2 Hz, 10.1 Hz, 1H).

References (Experimental):

1. Alacid, E.; Najera, C. *J. Org. Chem.* **2008**, 73, 2315-2322.
2. Mori, M.; Takimoto, M. *J. Am. Chem. Soc.* **2001**, 123, 2895-2896.

3. Fillion, E.; Dumas, A. M.; Hogg, S. *J. Org. Chem.* **2006**, 71, 9899-9902.

4. Cahiez, G.; Habiak, V.; Gager, O. *Org. Lett.* **2008**, 10, 2389-2392.

5. Block, E.; Jeon, H. R.; Putman, D.; Zhang, H-G. *Tetrahedron* **2004**, 60, 7525-7541.

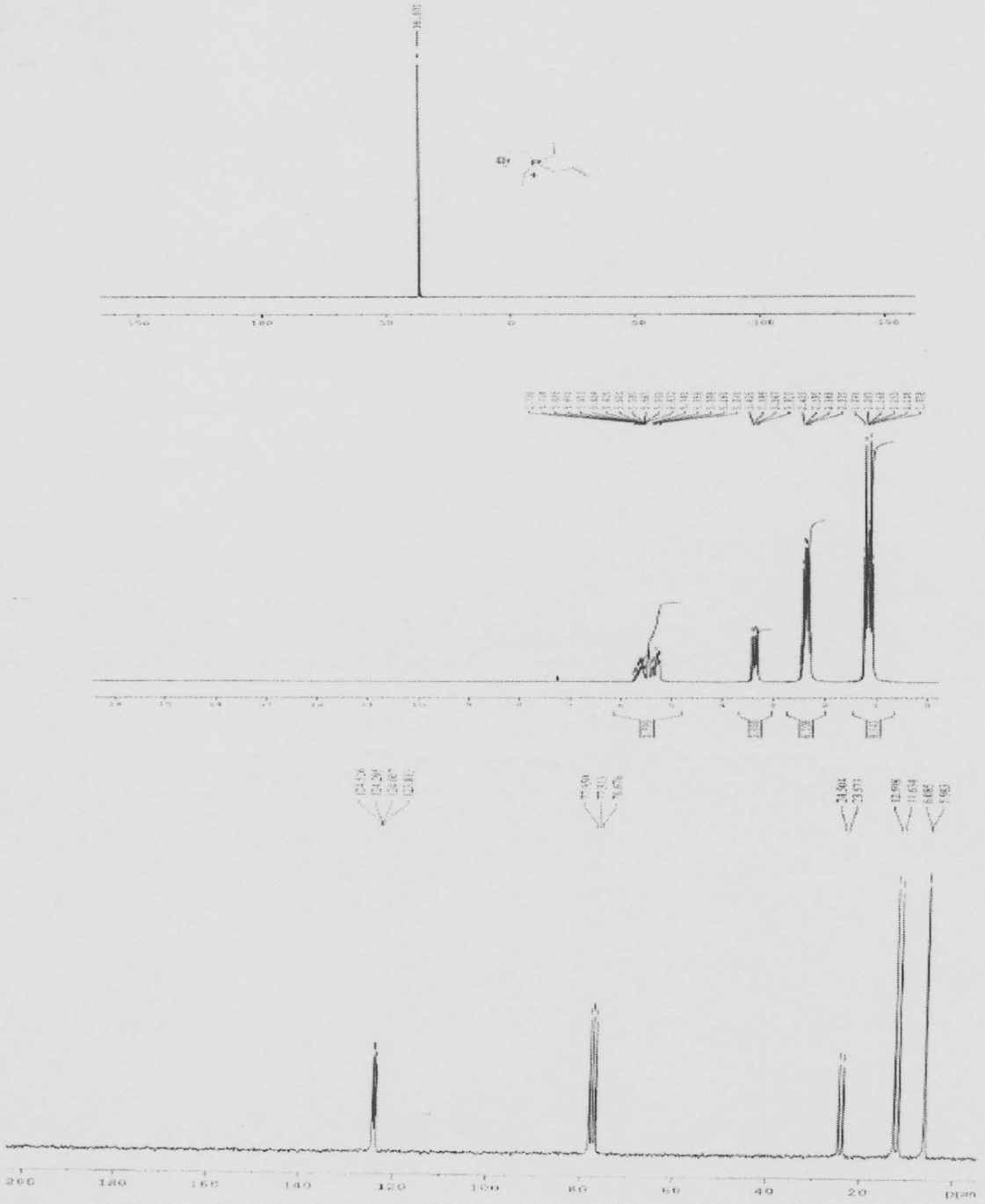
6. Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, 43, 723-730.

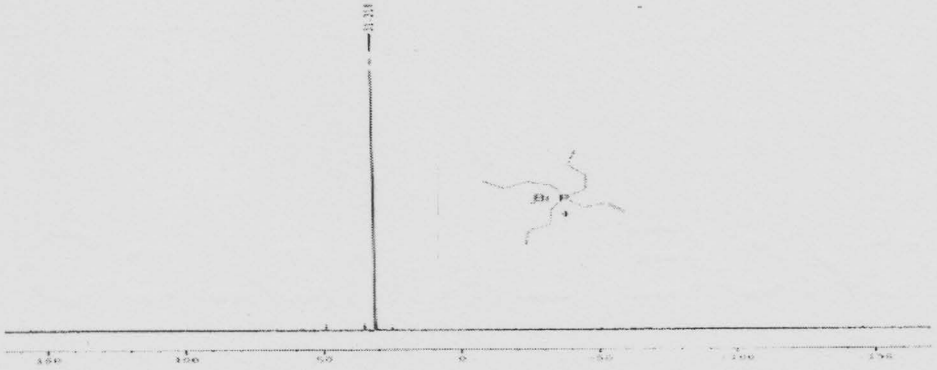
7. Che, C-M.; Chen, J. *Angew. Chem. Int. Ed.* **2004**, 43, 4950-4954.

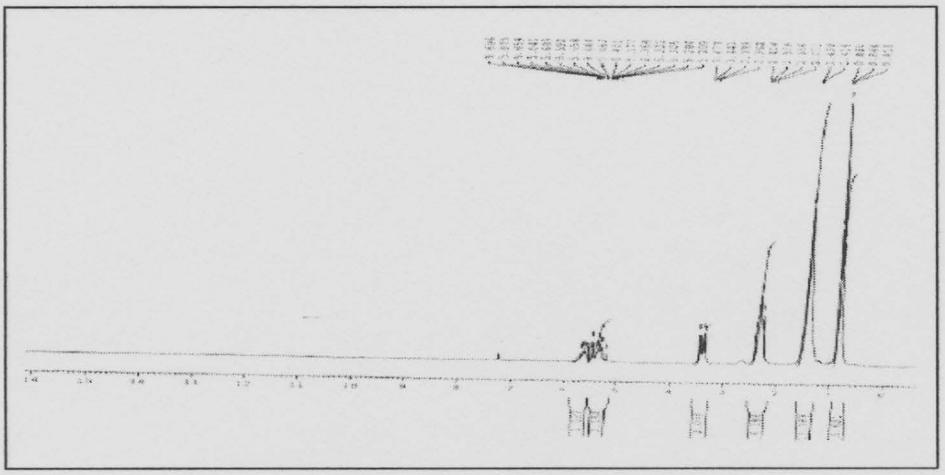
8. Auge, J. *Tetrahedron Lett.* **1985**, 26, 753-756.

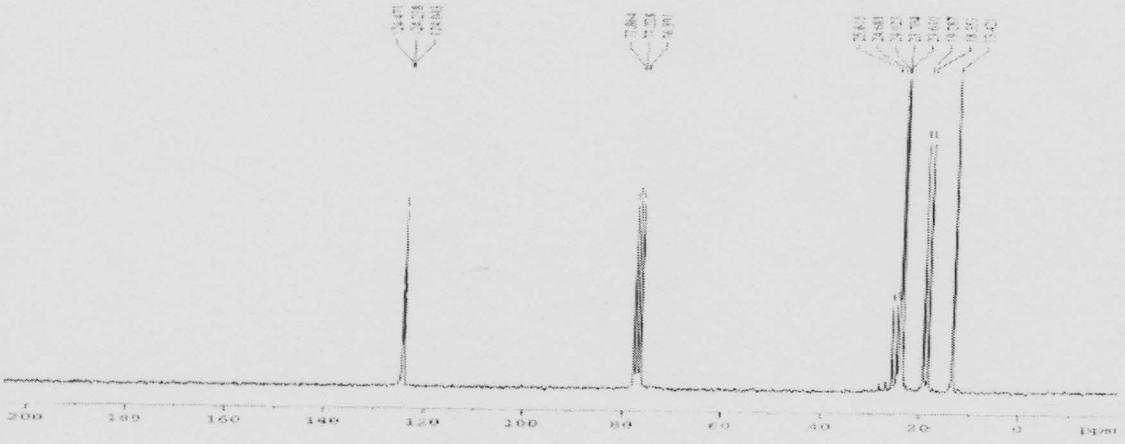
9. Habrant, D.; Stengel, B.; Meunier, S.; Mioskowski, C. *Chem. Eur. J.* **2007**, 13, 5433-5440.

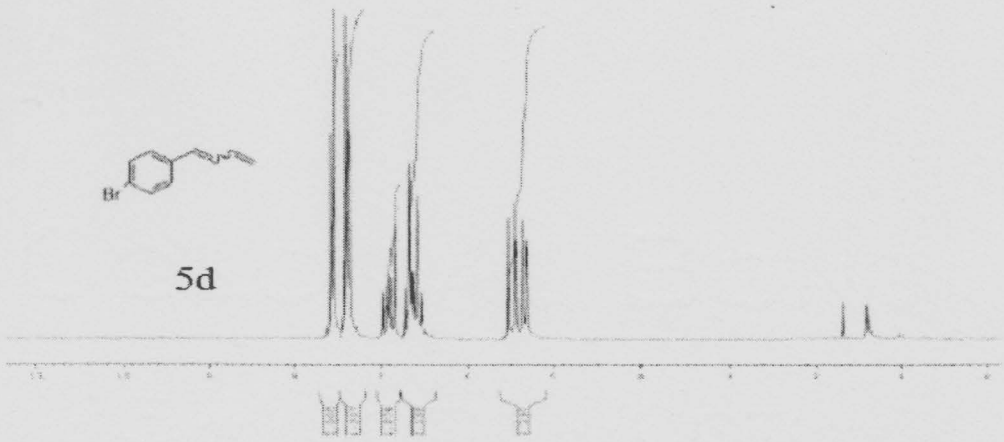
NMR Spectra of New Compounds:

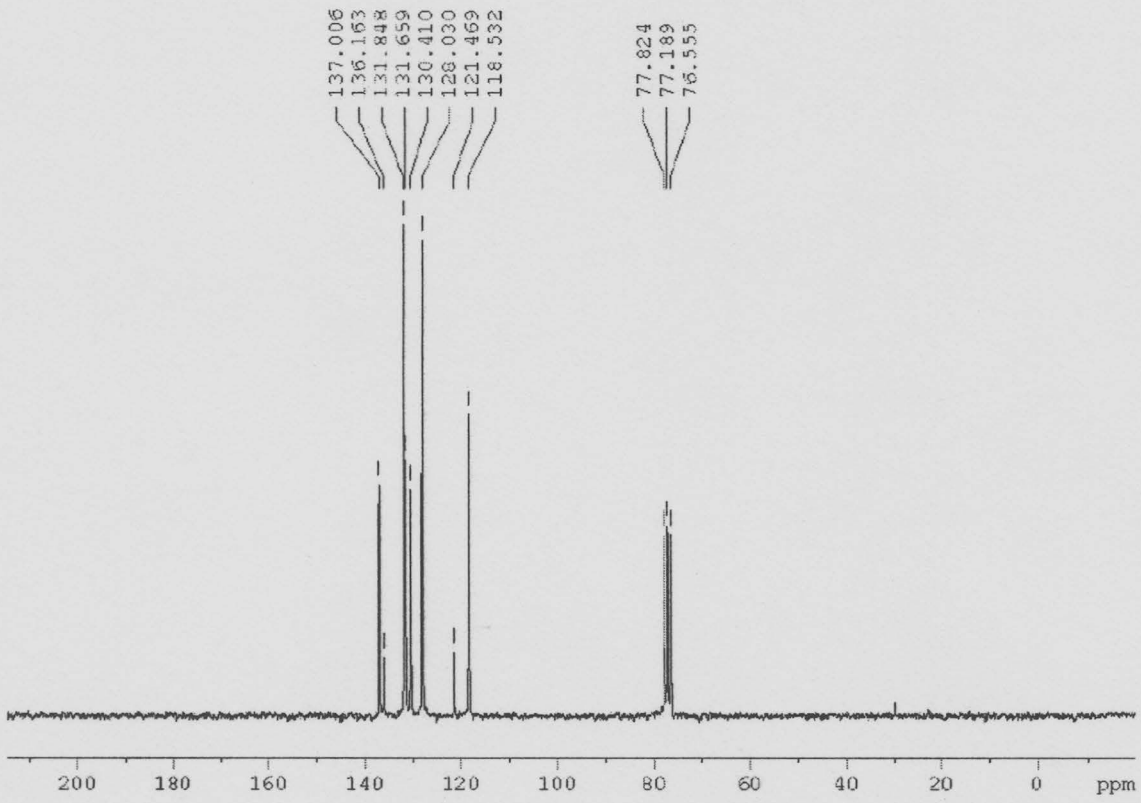


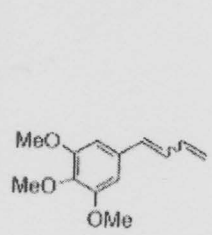






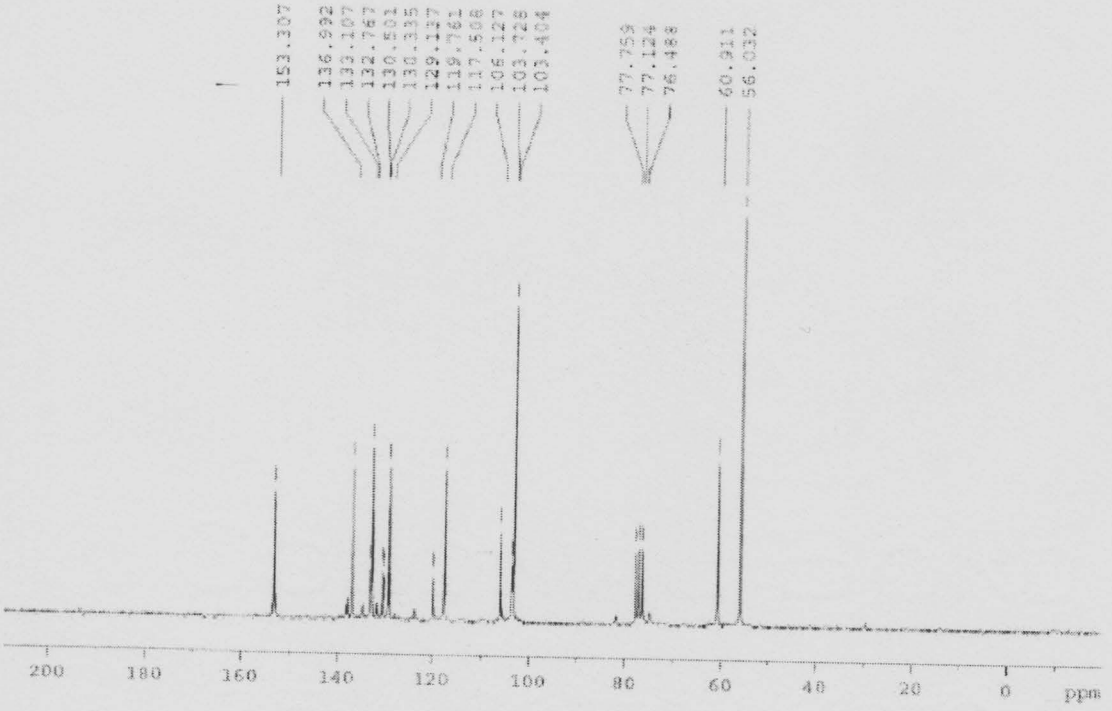

Br
5d

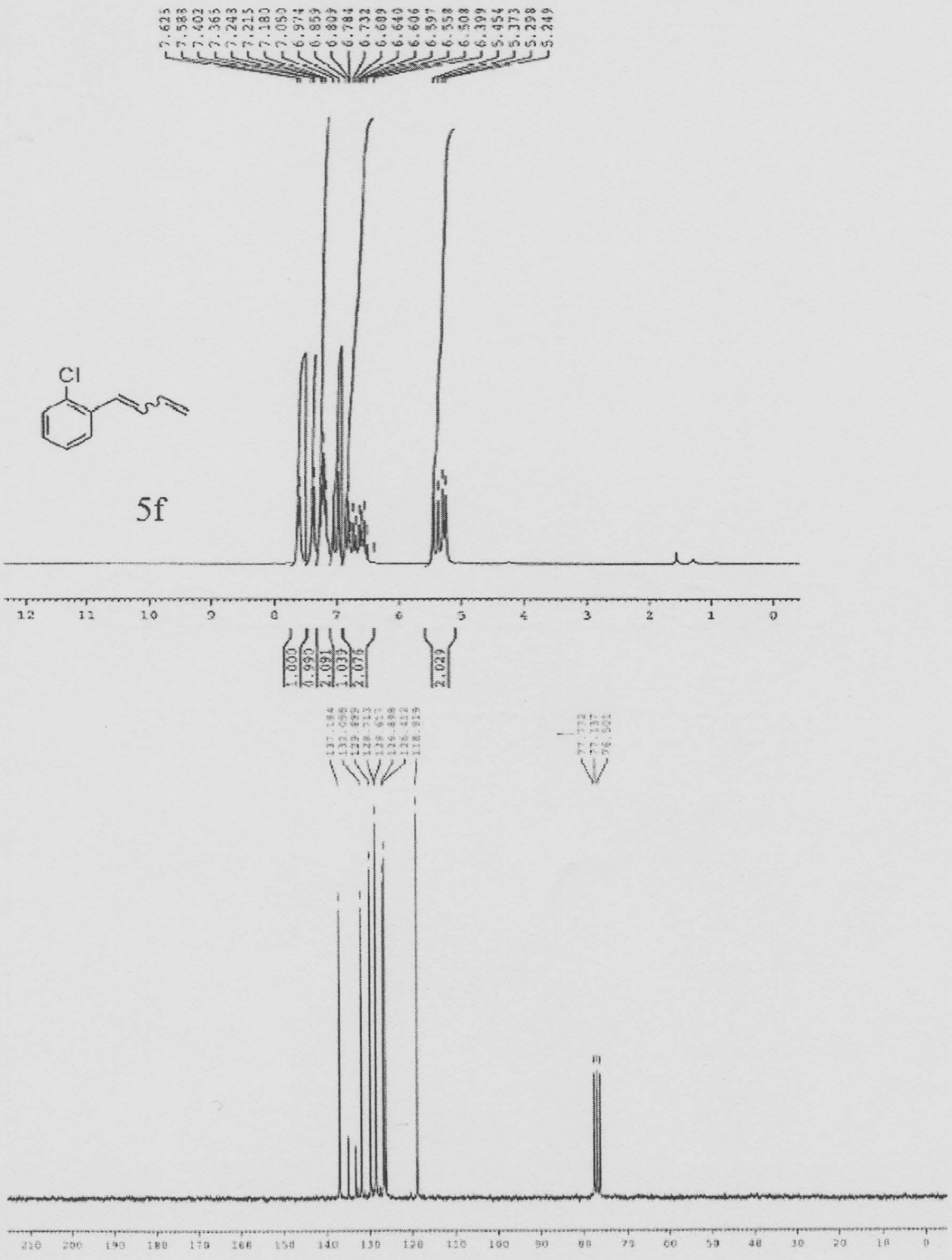

137.006
136.163
131.848
131.659
130.410
128.030
121.469
118.532
77.824
77.189
76.555
200
180
160
140
120
100
80
60
40
20
0
ppm

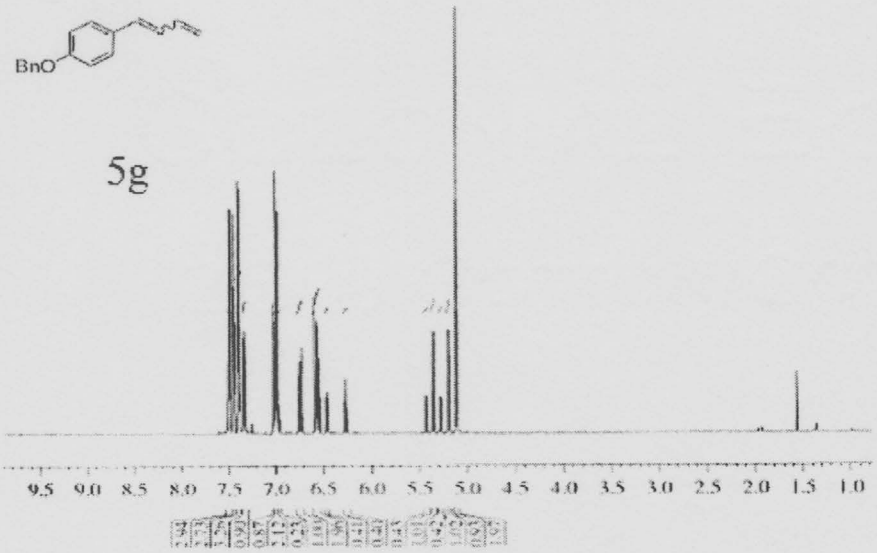

MeO
MeO
OMe

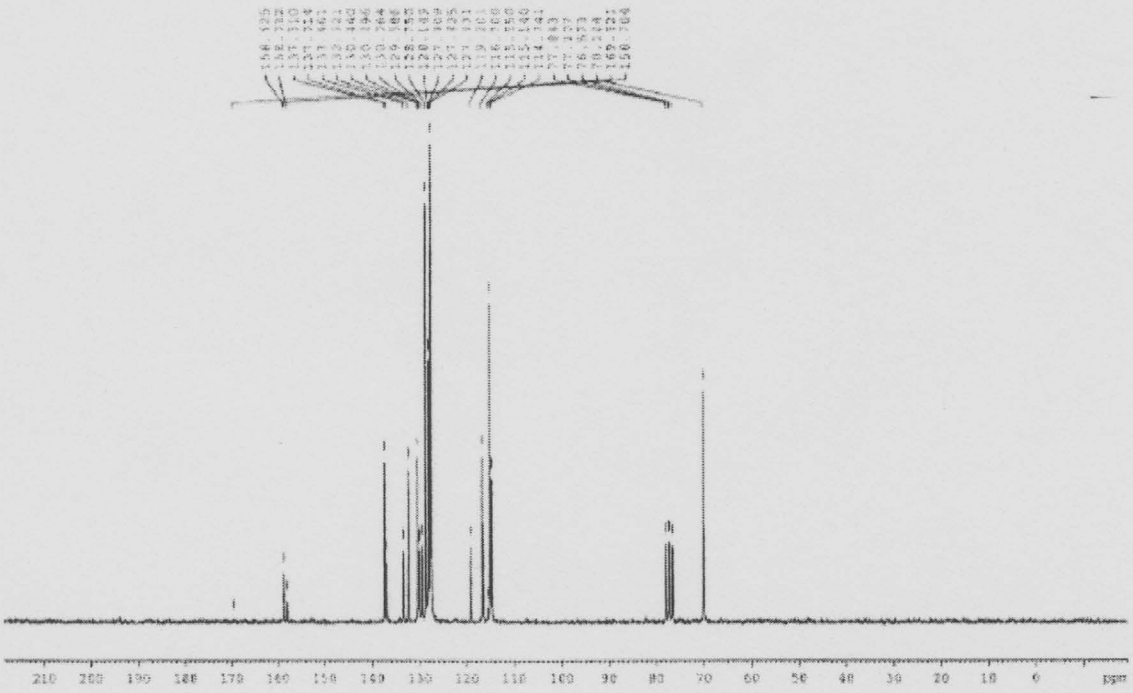
5e

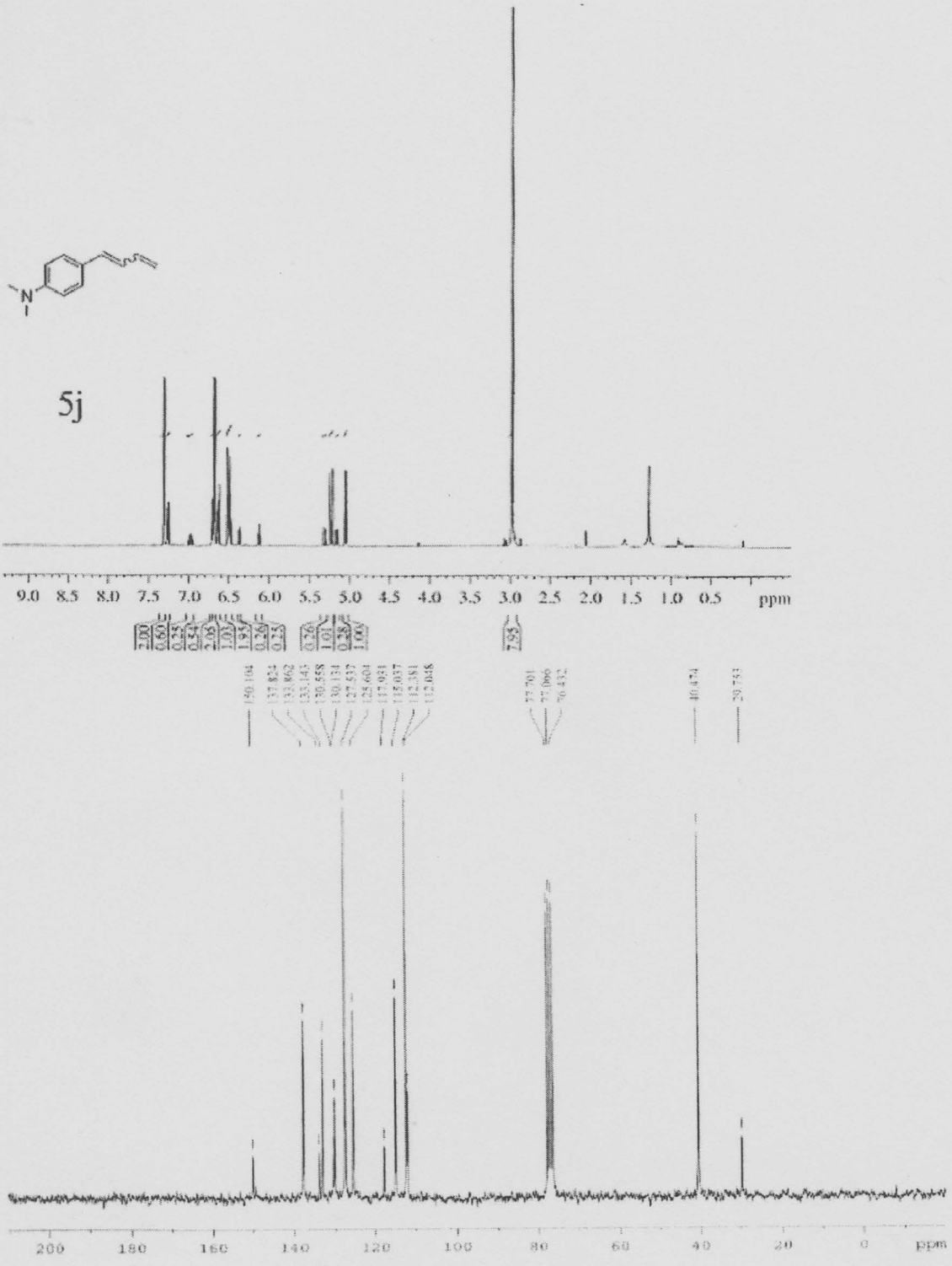
9
8
7
6
5
4
3
2
1
ppm

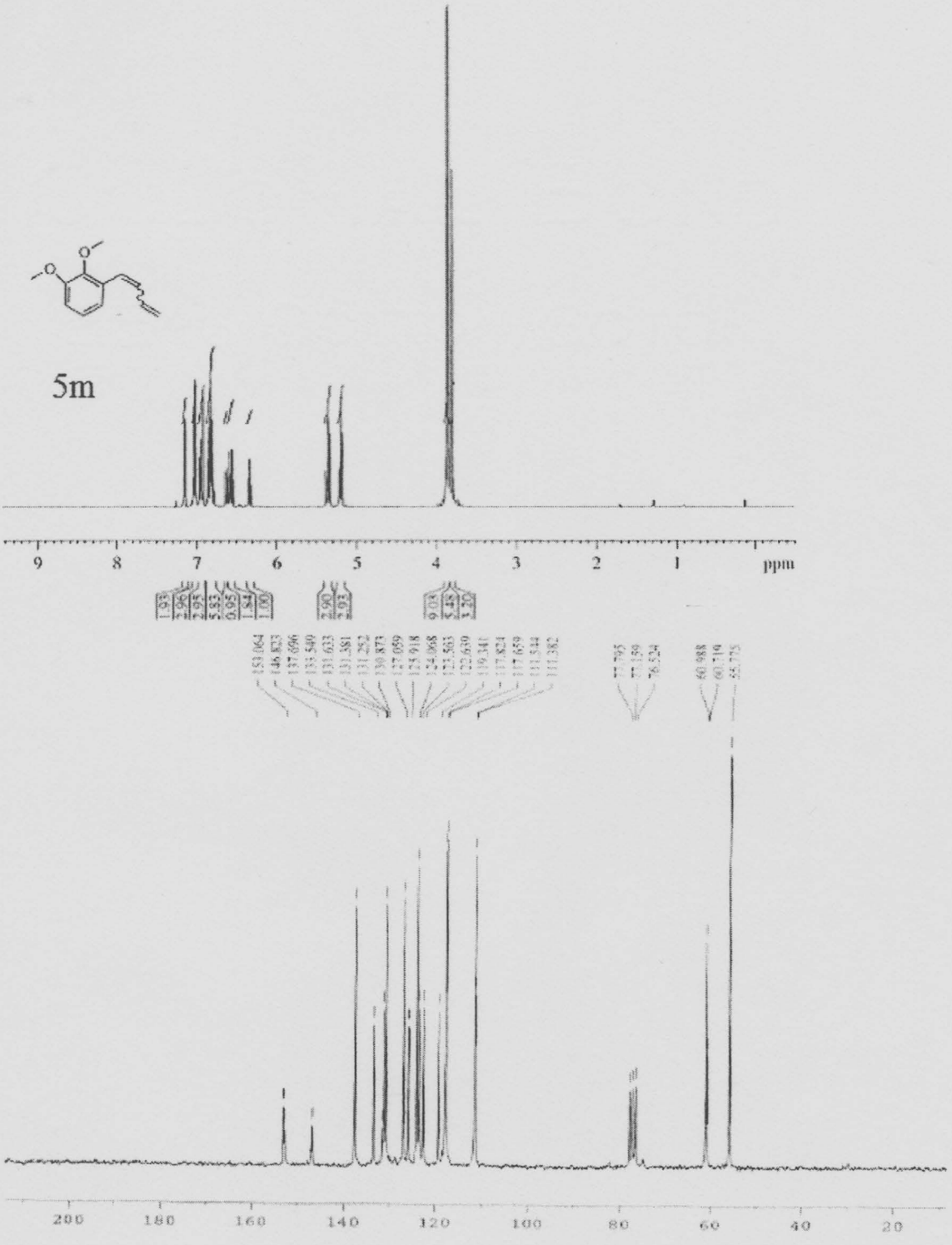

153.307
136.992
133.107
132.767
130.503
130.335
129.137
119.781
117.508
106.127
103.728
103.404
77.759
77.124
76.488
60.911
56.032
200
180
160
140
120
100
80
60
40
20
0
ppm

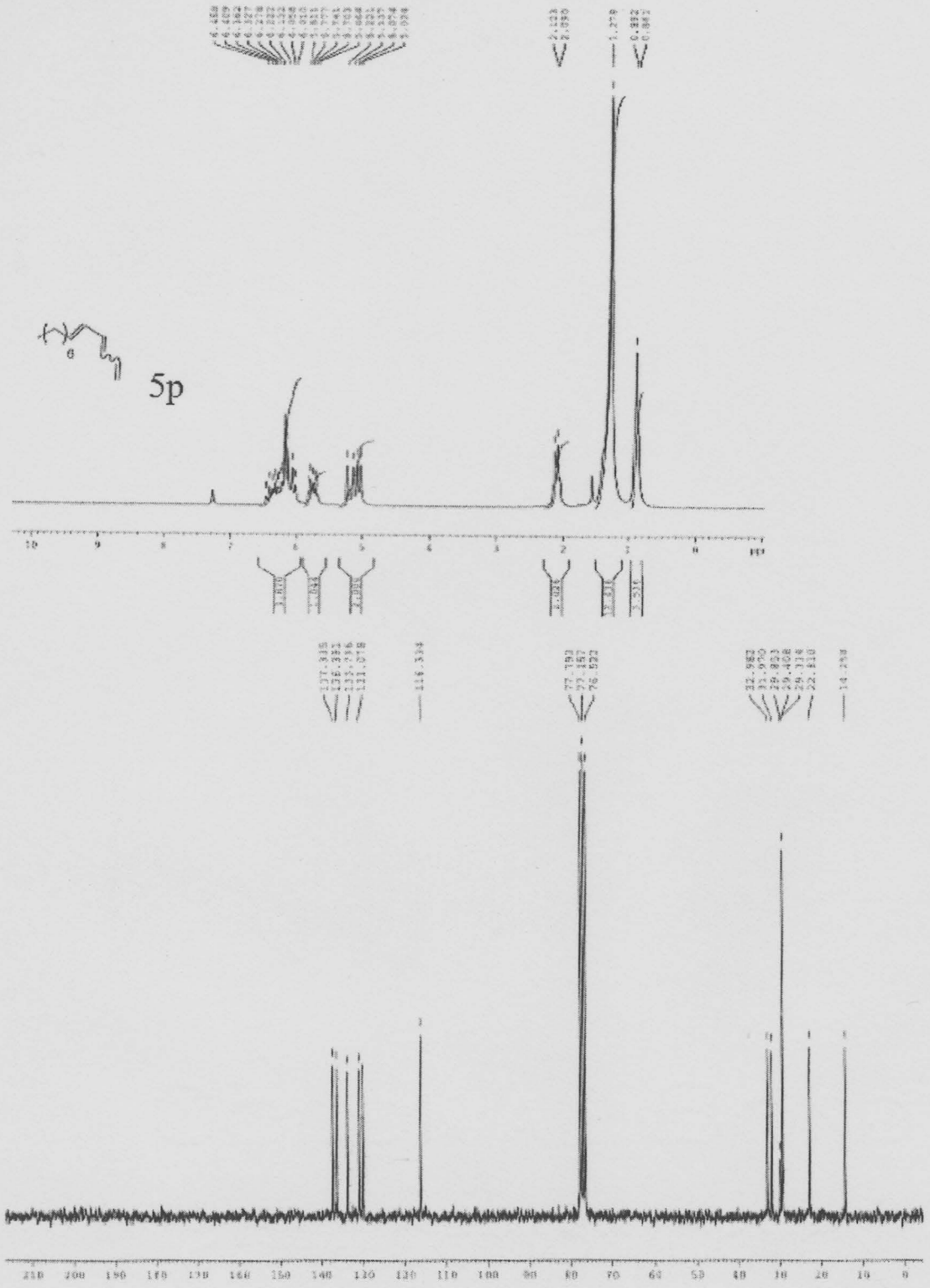

Cl
5f

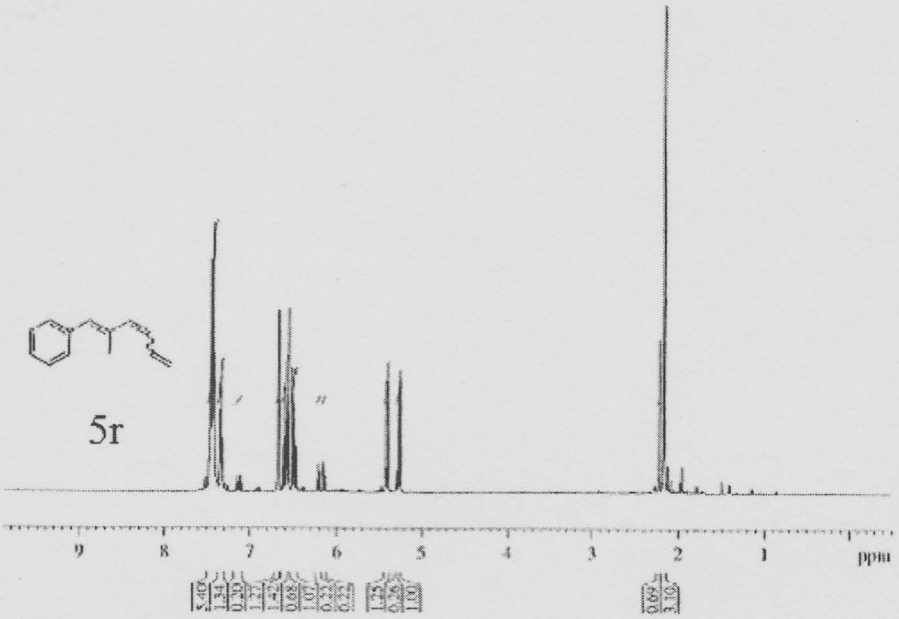

BnO
5g
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0

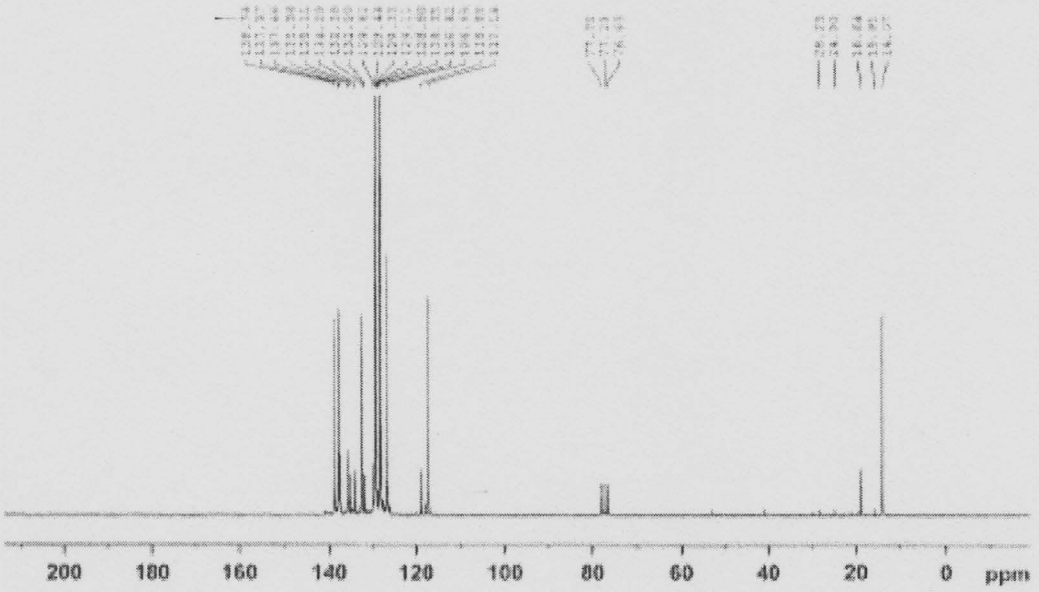

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


5j
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
200 180 160 140 120 100 80 60 40 20 0 ppm


5m
9
8
7
6
5
4
3
2
1
ppm
200
180
160
140
120
100
80
60
40
20


5p


5r
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

Conclusion

In conclusion, an efficient stereoselective method for the synthesis of α-phosphonoenamines based on a modified Peterson olefination was developed. The carbanion derived from diethyl 1-dimethylamino-1-trimethylsilylmethanophosphonate was shown to react generally with aromatic or aliphatic aldehydes selectively eliminating in Peterson fashion (as opposed to HWE fashion) to deliver functionally rich α-phosphonoenamines. These intermediates could by hydrolyzed under acidic conditions yielding homologated carboxylic acids. A second highly efficient method was developed for this one-carbon homologation of aldehydes to carboxylic acid derivatives. In this case, the reaction of a 1,1-*bis*-dimethylphosphonate derivative with an aldehyde was shown to yield the same α-phosphonoenamine intermediates as above in high yield. These were also hydrolyzed under acidic conditions using HBr to give homologated acids. This two-step process was optimized into a one-pot protocol allowing for the most efficient conversion to date of the aldehyde to homologated carboxylic acid interconversion.

The reaction of bis(trimethylsilyl)chloromethane with *s*-BuLi was found to proceed chemoselectively via a transmetallation route (lithium halogen exchange) rather than deprotonation yielding a nucleophilic bistrimethylsilylmethyl anion quantitatively. This bis-silylated intermediated was shown to react readily with aldehydes providing a general entry to vinylsilanes via Peterson-type elimination.

The reaction of α–silylated ylides was then investigated with non-enolizable aldehydes and shown for the first time to proceed via selective Peterson-type elimination providing a direct route to synthetically useful vinylphosphonium salts. This reaction proved to be of considerable mechanistic interest as prior literature reports describe Wittig-type elimination from α–silylated ylides yielding vinylphosphonium salts. These prior studies are consistent with an oxaphosphetane intermediate undergoing normal Wittig-type elimination and do not require the intermediacy of a betaine-type species. These prior studies employ distilled, salt-free ylides. Our work shows that a catalytic amount of lithium salt (or presumably other cations) can alter the nature of the reaction considerably. In this case, there can be no doubt of the involvement of a betaine as the Peterson-type elimination that we observed would require either direct betaine formation, or polar opening of an initial kinetically formed oxaphosphetane intermediate.

The chemoselective formation of trialkylbenzyl phosphoranes in water and their Wittig reaction with aromatic and aliphatic aldehydes was demonstrated for the first time. This process provided a practical, stereoselective and environmentally benign route to valuable *trans*-stilbenes and alkenes. An application of this method for the synthesis of the phytoalexin resveratrol was described. In addition, the method allowed for a gram-scale synthesis of the anticancer agent DMU-212 utilizing no organic solvent at any stage. The triethylphosphine oxide side product produced in this Wittig reaction is water soluble and the stilbene products were isolated by simple suction filtration and washing with water. The use of trialkyl groups on phosphorus is known to provide higher levels of (*E*)-olefin selectivity on reaction with aldehydes. Hence we were able to solve two of the

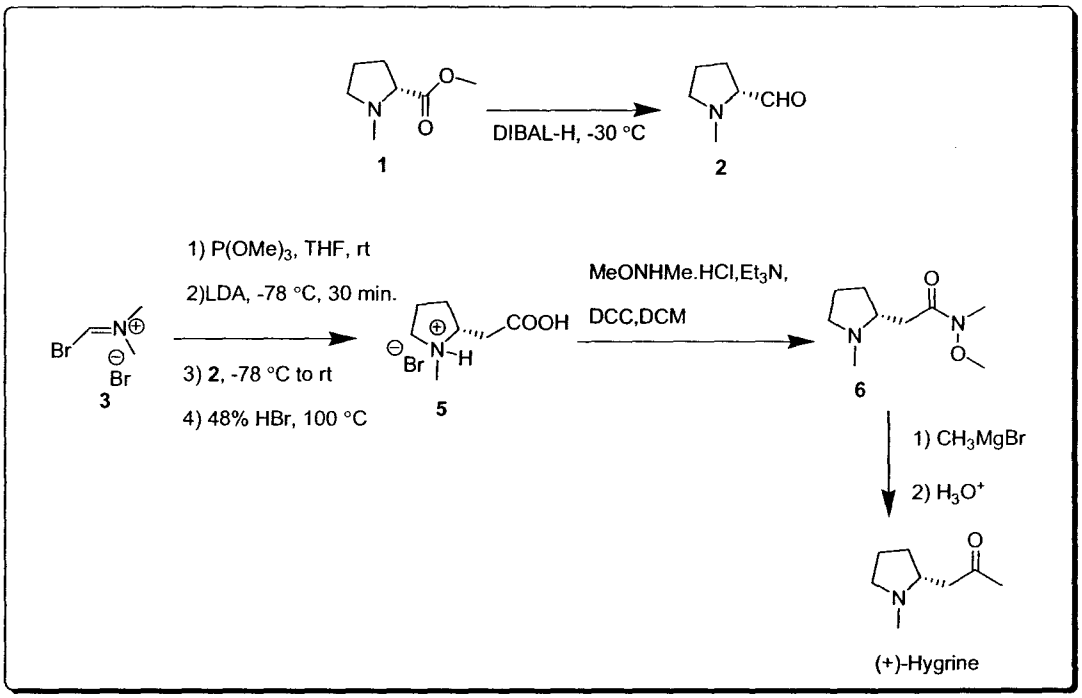
problems inherent to the synthesis of alkenes from semi-stabilized benzylidenyl ylides. The use of triethylphosphine derived ylides allows both for high (*E*)-olefin stereoselection as well as easy phosphine oxide side product removal. A large number of trans-stilbenes and other 1-phenyl alkenes were produced using this new aqueous method.

As an extension of the above method, a direct synthesis of 1,3-dienes and 1,3,5-trienes from the reaction of semi-stabilized triethylallylphosphonium derived ylides was also investigated in water. These species were shown to react with a range of saturated and unsaturated aldehydes in water as solvent, employing sodium hydroxide as base. The water soluble phosphine oxide side product was removed simply by aqueous partitioning of the organic products. The same ylides were also shown to react with enolizable aliphatic aldehydes under these conditions, normally expected to give homo-aldol or Cannizzaro-type side products. This method allowed for the synthesis of a wide range of substituted 1,3-dienes and 1,3,5-trienes. A mechanistic hypothesis involving the formation of phosphonium salt stabilized micelles was presented to explain the high chemoselectivity observed favouring the Wittig process.

Future Work

The work described in the present PhD thesis can serve as the groundwork for various future novel transformations, applications and/or mechanistic investigations. For example, the homologation methodology described in chapter two could potentially be applied towards a total synthesis of the alkaloid Hygrine as outlined in Scheme 1.

Hygrine is present in coca leaves and has been the subject of several pharmacological studies.[1] It is the precursor for more complex alkaloids including hyocyamine and scopolamine, both of which are of interest in a number of medicinal products.



Scheme 1. Total Synthesis of (+)-Hygrine

The total synthesis would start from the commercially available ester **1.** A controlled DIBAL-H reduction of the ester at –78 °C will give N-methylprolinal **2.**[2] Using the methodology described in chapter two, the aldehyde **2** will be homologated to the N-

methyl homoproline hydrobromide salt **5**, which will subsequently be converted to **6** under Weinreb amide formation condition. The total synthesis will be finished via an addition of methylmagnesium bromide to **6** giving hygrine in only 4 overall steps.

The present work described in chapter three has some remaining issues that need to be addressed in the future. Notably, the present method only affords moderate (*E*) stereoselectivity. Thus, it will be interesting to see whether one can get vinylsilanes with complete (*E*) stereoselectivity by looking at salt effects and/or solvent effects. Another area of potential interest would be to design new silicon based reagent to obtain vinylsilanes with high (*Z*) stereoselectivity. It is not clear how this could be achieved; nonetheless we note the significant successes that have been advanced in (*Z*)-selective Horner-Emmons olefination chemistry employing the fluorinated Still-Genari[3] reagent or the Ando method.[4] This work inspires confidence that a hybrid methodology could be elaborated towards realization of a complementary (Z)-vinylsilane synthesis protocol.

The vinylphosphonium salt synthesis as described in chapter four could also benefit from further mechanistic investigations. In the present work, it was proposed that the oxaphosphetane ring opens up in presence of lithium salt to give betaine intermediate. The betaine then undergoes free rotation and subsequent synperiplanar elimination to give vinylphosphonium salt. It would be interesting to see whether one can detect the betaine intermediate via low temperature NMR experiments. Various salt and/or solvent effects on the stereoselectivity of vinylphosphonium salt synthesis could also be looked

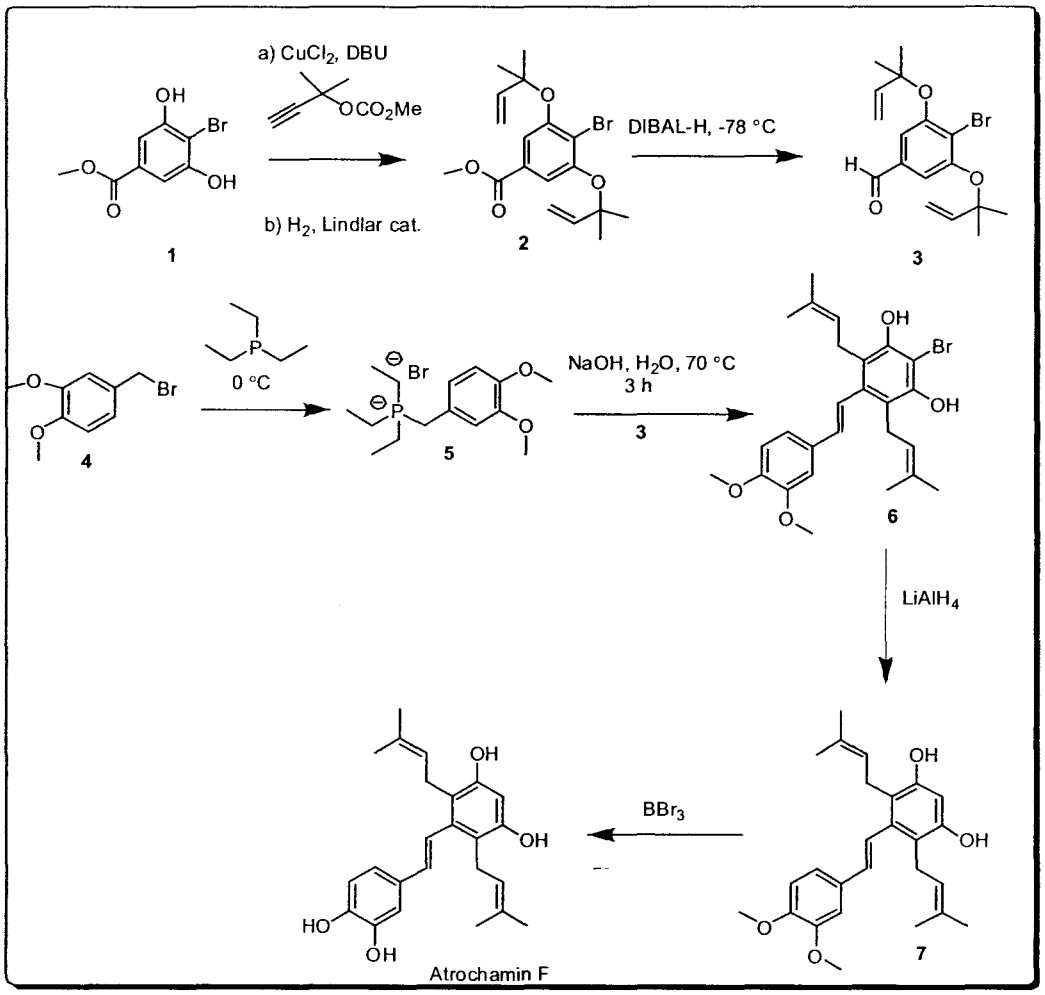
at. We believe that a full understanding of the mechanisms of the Wittig reaction has yet to be achieved.

The aqueous Wittig chemistry described in chapters five and six also could benefit from further mechanistic investigations. In the present thesis it was proposed that micelles are being formed under the experimental conditions and these micelles are suppressing the side reactions. This explanation fits with the physical observations during the course of the reaction and empirically with the chemoselectivity that is observed. In the future, experimental data will be required to support or refute the micellular hypothesis.

The aqueous Wittig chemistry based stilbene synthesis has potentially many applications in the total synthesis of natural products, material sciences, photovoltaics etc. For example, the present method can be used for an efficient total synthesis of stilbene based natural product[5] Atrochamin F as shown in Scheme 2.

Atrochamin F was isolated from the stem of *Atrocarpus chama*[6] along with structurally more intriguing atrochamins H, J and I. These prenylated stilbenes have shown weak cytotoxic activities.

The total synthesis would start from the readily available ester **1**. As shown in the Scheme 2, copper-mediated etherification[7] of ester **1** with dimethylpropynyl carbonate coupled with catalytic hydrogenation using Lindlar's catalyst will give **2**. A controlled DIBAL-H reduction at –78 °C will give the aldehyde **3**. The required phosphonium salt **5** would be obtained from the commercially available 3,4-dimethoxybenzyl bromide **4** using the methodology described in chapter five of this thesis.

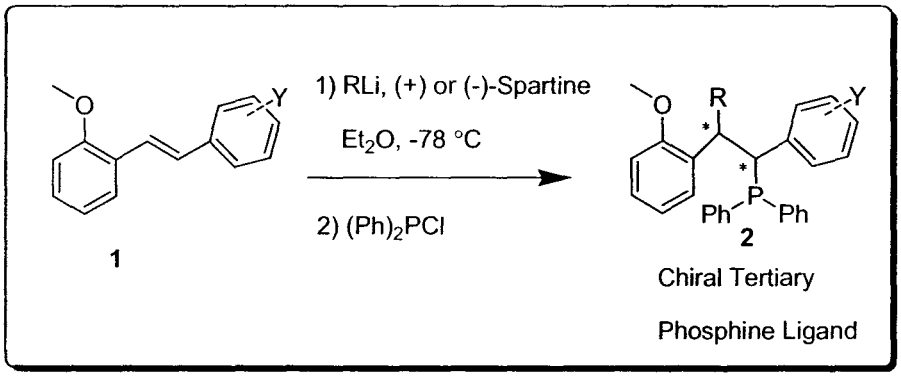


Scheme 2. Total Synthesis of Atrochamin F

A subsequent aqueous Wittig[8]-Claisen rearrangement[9] cascade will be the key step towards the total synthesis of Atrochamin F. Product of the said cascade reaction would be the stilbene **6**, which would then be debrominated by the action of $LiAlH_4$ to afford **7**. Finally, a double demethylation using BBr_3 will give Atrochamin F in 6 overall steps.

The aqueous Wittig chemistry can also be extended to other semistabilized ylide systems for the synthesis of vinyl ethers, vinyl sulfides and vinyl halides with high stereoselectivity.

Another fascinating possibility would be to use stilbenes as substrates for carbolithiation chemistry[10]. Asymmetric Addition of organilithium reagents across the double bond of stilbenes using (+) or (-)-Spartine as ligand followed by electrophlilic quenching with $(Ph)_2PCl$ can potentially afford highly valuable chiral tertiary phosphine ligands as shown in Scheme 3.



Scheme 3

Lastly, the aqueous Wittig chemistry can be tied up with medicinal chemistry studies. For example, various substituted stilbenes and/or dienes can be synthesized on the aqueous Wittig manifold and those compounds can be screened against various cancer cell lines to uncover biologically active hits via high throughput screening.

References:

1. (a) Berkov, S.; Zayed, R.; Doncheva, T. *Fitoterapia* **2006**, 77, 179-182. (b) Jordan, M.; Humam, M.; Bieri, S.; Christen, C.; Poblete, E.; Munoz, O. *Phytochemistry* **2006**, 67, 570-578. (c) Vitale, A.; Acher, A.; Pomilio, A. *J. Ethanopharmacol.* **1995**, 49, 81-89.
2. Garcia-Arevalo, E. B.; Colmenares, J. C. Q. *Tetrahedron. Lett.* **2008**, 49, 3995-3996.

3. Still, W. C.; Gennari, C. *Tetrahedron. Lett.* **1983**, 24, 4405-4408.

4. Ando, K. *J. Org. Chem.* **1997**, 62, 1934-1939.

5. Tao, S.; Xiao-Ning, W.; Hong-Xiang, L. *Nat. Prod. Rep.* **2009**, 26, 916-935.

6. Wang, Y. H.; Hou, A. J.; Chen, D. F.; Weiller, M.; Wendel, A.; Staples, R. J. *Eur. J. Org. Chem.* **2006**, 15, 3457-3463.

7. Godfrey, J. D.; Jr. Mueller, R. H.; Sedergran, T. C.; Soundarrajan, N.; Colandrea, V. *Tetrahedron. Lett.* **1994**, 35, 6405-6408.

8. McNulty, J.; Das, P. *Eur. J. Org. Chem.* **2009**, 4031-4035.

9. Naraya, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, 44, 3275-3279.

10. Hogan, L. A. M.; O'Shea, D. F. *Chem. Commun.* **2008**, 3839-2851.