SALTS IN ORGANIC SYNTHESIS

NEW APPLICATIONS OF PHOSPHONIUM SALTS IN ORGANIC SYNTHESIS

New Trialkylphosphoranes (Ylides) for Wittig Olefination

Isolation and Purification of Flavonoids

By

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A Thesis

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ABSTRACT

This thesis describes the development of the Wittig olefination reaction of stabilized, semistabilized allylic trialkylphosphorus ylides with various aldehydes to afford *E* olefins mainly (*E*>89%). Since the steric demand of trialkylphosphorus ylides was decreased, aldehydes achieved high *E* selectivity. On the other hand, predominant or exclusive formation of *Z* olefins was achieved by using allylic triphenylphosphorus ylides and aromatic aldehydes like benzylaldehyde, while the combination of allylic triphenylphosphorus ylides and such sterically hindered aldehydes as cyclohexanecarboxaldehyde led to *E* olefin formation upon ylide formation with LiHMDS. In the case of olefination reactions of aldehydes with dimethyl thiazole ylide, it was shown that among the aromatic aldehydes only 4-nitrobenzaldehyde reacted with this ylide and provided a pure *E* olefin product (41% yield). Dimethylmalonyltributylphosphorane (DMTP) reacted with aromatic aldehydes in toluene at 125 °C to give the corresponding alkenes. 4-Nitrobenzaldehyde gave the alkene in a much higher yield (81%), followed by 4-chlorobenzaldehyde (31%). With benzaldehyde, the corresponding olefin was isolated in only 14% yield under these conditions. Clearly, this highly stabilized ylide only enters into reaction with electron deficient aldehydes. A possible approach to *Z*-α, β-unsaturated aldehydes was investigated through the olefination of an acetal-ylide followed by hydrolysis. However, *E* acetal olefins were in fact isolated from this 2'-(1,3-dioxolanyl)-triethylphosphorus ylide with aromatic aldehydes in good yields (62%-76%). This result is still mechanistically interesting in view of the chemoselective formation of such an ylide in the presence of three ethyl substituents on phosphorus.

Class of flavonoids: Sakuranetin, Naringenin and (2*S*)-7-methoxy-6-hydroxyflavanone, have been isolated from the diseased bark of *Prunus sp.* The structures were elucidated based on the spectroscopic data. Locations of 4-keto, 5-OH and 7-methoxy were deduced from COSY and HMBC spectra. Such compounds are of interest for their potential antibiotic activity against vancomycin-resistant strains of microbes.

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ABBREVIATIONS

Ac	acetyl
COSY	Correlation Spectroscopy
Bu	butyl
$CDCl_3$	deuterated chloroform
CD_3OD	deuterated methanol
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBALH	diisobutylaluminum hydride
DMTP	dimethylmalonyltributylphosphorane
Et	ethyl
EWG	electron withdrawing group
FTIR	Fourier Transform Infrared
HMBC	Heteronuclear Multiple Bonds Coreelation
KHMDS	Potassium bis(trimethylsiyl)amide
LiHMDS	Lithium bis(trimethylsiyl)amide
MDR	multidrug-resistant
MS	Mass Spectrometry
NaHMDS	Sodium bis(trimethylsiyl)amide
Na_2SO_4	sodium sulphate
NMR	Nuclear Magnetic Resonance
OPA	Oxaphosphetane
PhMe	toluene
THF	tetrahydrofuran
TLC	thin layer chromatography

Chapter 1

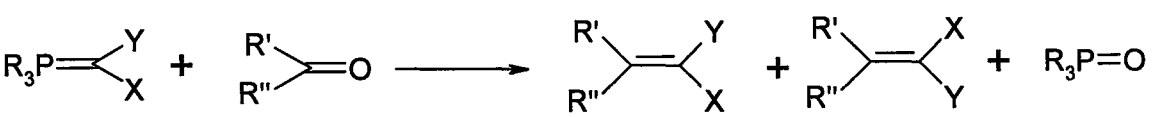
New Trialkylphosphoranes (Ylides) for Wittig Olefination

Introduction

1.1. The evolution of the Wittig reaction

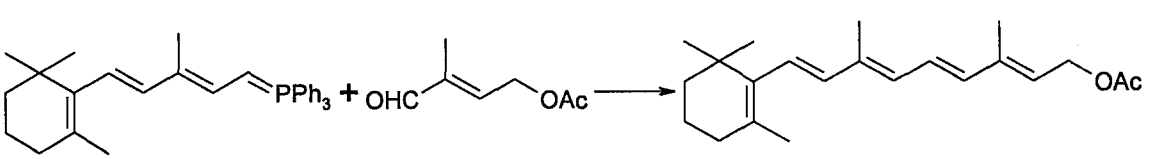
The Wittig reaction is very valuable in the construction of organic molecules as it generates a double bond, generally with high levels of geometric control.[1] It involves the condensation of an ylide with a carbonyl compound to give an olefin, eliminating a phosphine oxide (Equation 1).

Equation 1. General Wittig olefination reaction



Although Staudinger and coworkers[2] reported a carbonyl olefination reaction using a phosphorus ylide in 1918, Wittig and his students generalized the reaction and brought it to wide attention in the early 1950s.[3] Because of its effectiveness and generality, the Wittig reaction has been applied rapidly in industrial synthesis and in natural product synthesis. The synthesis of vitamin A acetate in 1956, for example, was the first industrial application of the Wittig reaction (Equation 2).[4 (a)]

Equation 2. The synthesis of vitamin A acetate



Since then, applications of the reaction to both simple and very complex structures have appeared in the organic chemistry literature.[4] The Wittig reaction has evolved to allow regioselectivity and stereoselectivity in the introduction of the alkylidene group.

1.2. Mechanism and Stereochemistry of the Wittig reaction

Since Wittig proposed the mechanism for the Wittig reaction in 1953,[5] the reaction's character has attracted the attention of chemists for decades. Although chemists have attempted to arrive at a truly satisfying mechanistic explanation, some intimate details still remain to be elucidated.[6]

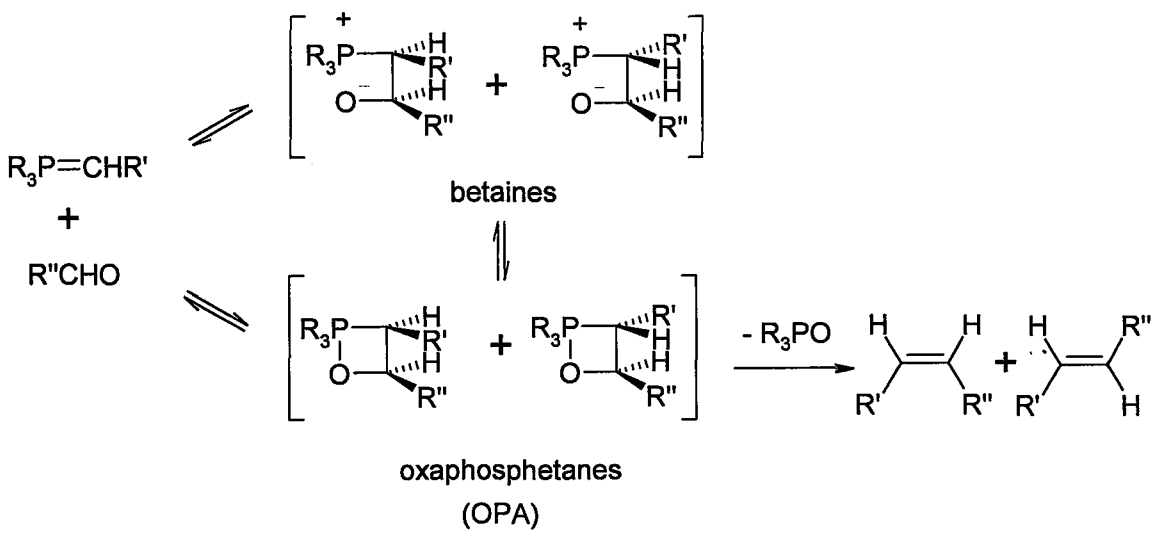
Stereochemistry is a powerful tool for probing the Wittig reaction process. As shown in Equation 1, the Wittig reaction can give one or both geometric isomers of the olefin products. The type of ylide and the exact reaction conditions play a key role in determining the reaction stereochemistry.[6] For example, nonstabilized phosphorus ylides ($Ph_3P{=}CHCH_3$ or $Ph_2RP{=}CHCH_3$) react with aldehydes to give largely *Z* alkenes, except under special conditions,[7, 8] and stabilized ylides ($Ph_3P{=}CHX$ or $Ph_2RP{=}CHX$, X= EWG) give predominantly *E* alkenes, but semistabilized ylides ($Ph_3P{=}CHX$ or $Ph_2RP{=}CHX$, X=benzyl or allyl) generally give a mixture of alkenes (*E*/*Z*=1/1).

Several mechanisms have been proposed for the Wittig reaction.[9] All of them seek to answer two key questions: 1) what intermediates predominate as the reaction proceeds from ylide and carbonyl compound to alkenes and phosphine oxide and 2) what mechanistic factors dominate the resulting stereochemistry.

The first mechanistic proposal was formulated by Wittig.[5] It gained broad acceptance in the 1960s. The mechanism was expressed by two steps including (a)

nucleophilic addition of the ylide carbanion to the carbonyl carbon to form a betaine species and (b) closure of the betaine to an oxaphosphetane (OPA), and decoposition of the oxaphosphetane to give alkene and phosphine oxide (Scheme 1).

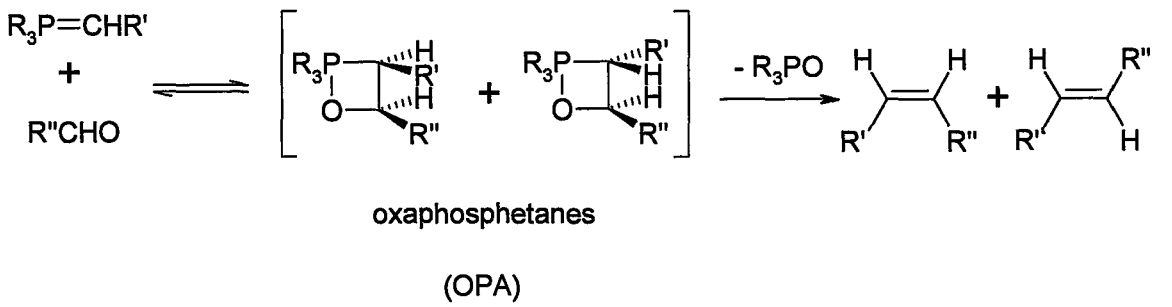
Scheme 1. Wittig mechanic proposal



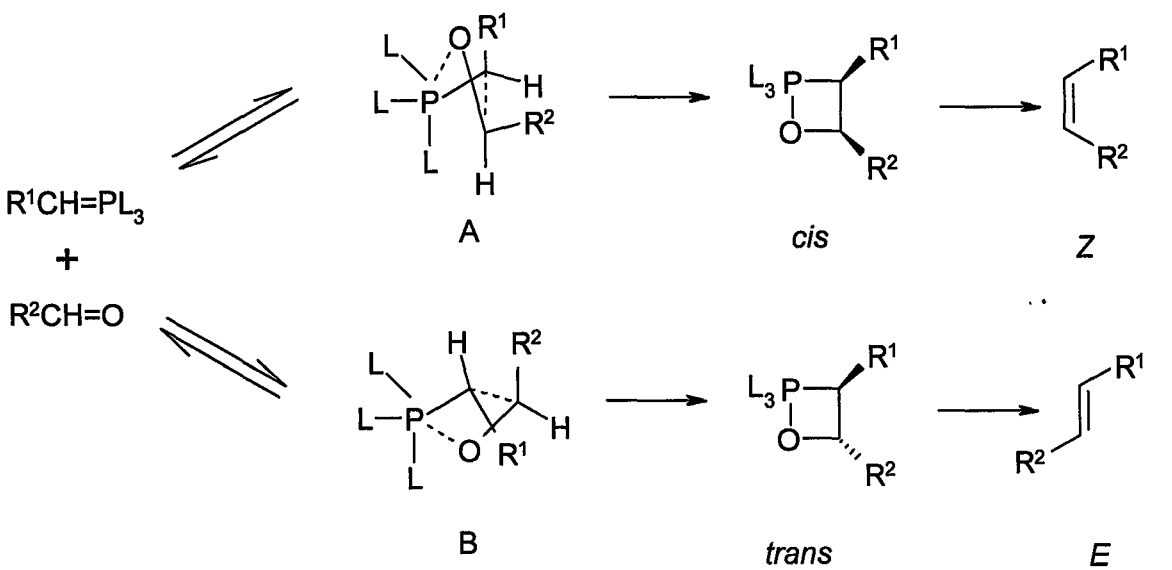
However, Wittig's proposal fell into disfavour after the work of Vedejs. The ^{31}P-NMR spectroscopic studies of Vedejs' group in 1973 indicated that 1,2-oxaphosphetanes could be reasonably persistent and that they should be considered as more important intermediates than betaines.[10] Furthermore, no betaine has been observed in a Wittig reaction. Subsequently, Vedejs[9 (c)] reported that 1,2-oxaphosphetanes were principal intermediates in a variety of reactions involving nonstabilized ylides and aldehydes and ketones. Schlosser[9 (a)] proposed "leeward" approach model. A 1,3–interaction in the transition state, leading to the oxaphosphetane, was the key to the *cis* geometry of the oxaphosphetane. This proposal relied on the propeller-like orientation of the phenyl groups about phosphorus. It also required a planar oxaphosphetane ring with C-C and P-O bond formation equally advanced. However, Recent studies of the Wittig reaction have

shown that the reaction proceeds through the oxaphosphetane intermediate and decomposition of oxaphosphetane to the product alkene (Scheme 2).[11]

Scheme 2. General mechanic proposal



Scheme 3. Vedejs' model



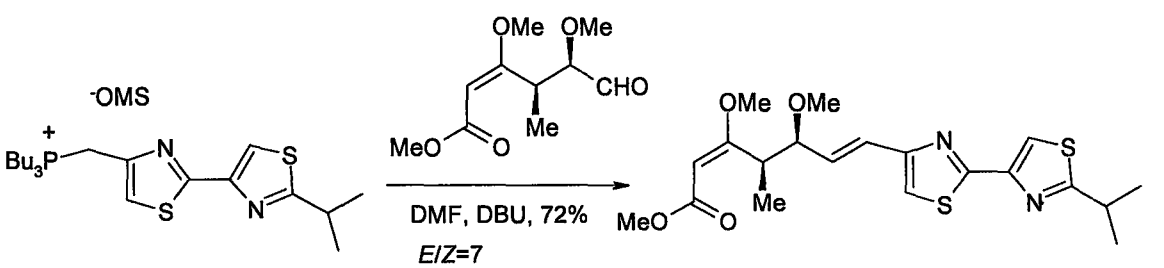
Vedejs[12] developed a model that included a four-center asynchronously-formed transition state, leading to the oxaphosphetane. It was proposed that the geometry of oxaphosphetane is the result of a balance of 1,2-and 1,3-interactions (Scheme 3). Vedejs' model also proposed that nonstabilized ylides have a transition state involving a "puckered" geometry and 1,3-interactions dominate to give lower energy for the *cis* oxaphosphetane and yield the *Z* olefin product. Stabilized ylides, whose transition states

involve a trigonal bipyamidal phosphorus atom, lead to trans-oxaphosphetanes and therefore *E*-alkenes. It appears to be the most useful tool for explaining the strong *cis* oxaphosphetane preference in many reactions of triphenylphosphorus nonstalized ylides, and the strong *E* selectivity in the kinetic reaction of stabilized ylides.[13]

1.3. Synthetic application of the Wittig reaction

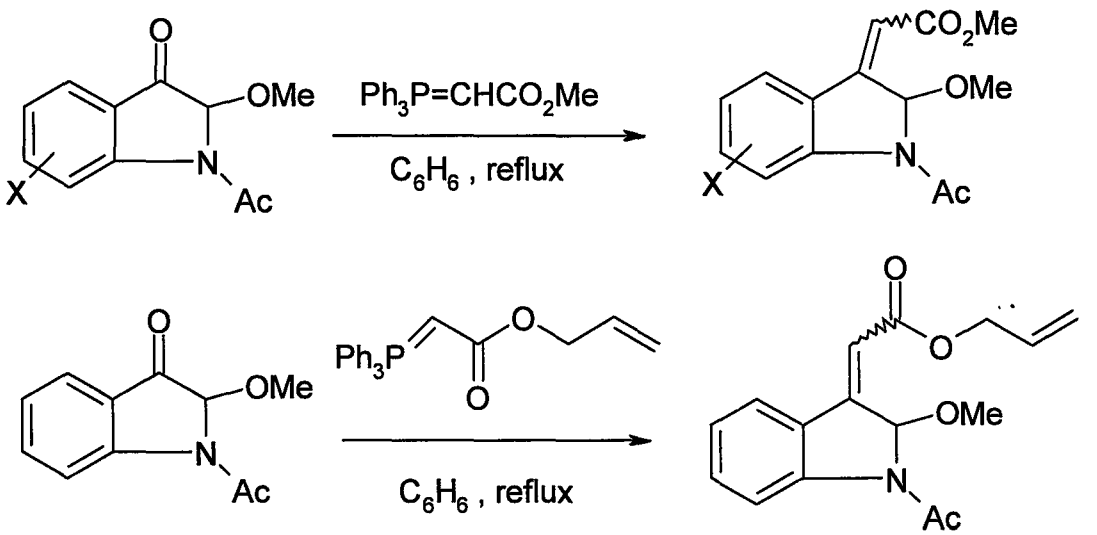
The Wittig reaction has been employed widely in organic synthesis because of its convenience, versatility and ease. Charette[14] employed a Wittig olefination in the final step of the total synthesis of (+)-Cystothiazole A (Equation 3), which is an antibiotic against fungi and cytotoxic against some human tumour cell lines. The reaction of a semistabilized tributylphosphonium salt and aldehyde in the presence of DBU at 0 °C gave a selectivity *E*/*Z* =7/1.

Equation 3. *E*-olefination in the synthesis of (+)-Cystothiazole A

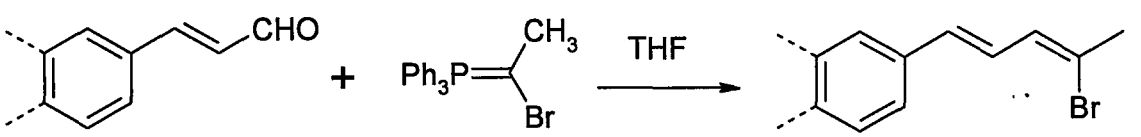


Two Wittig reactions were employed in the total synthesis of the anti-cancer reagent Dragmacidin A (Equation 4).[15] The first one gave a *Z*/*E* mixture (*Z*/*E*=7) of 3-alkylideneindoline in 98% yield. Very good *Z* stereocontrol (*Z*/*E*=11) was accomplished in the second Wittig olefination with a stabilized ylide.

Equation 4. *Z*-selectivity in the synthesis of Dragmacidin A



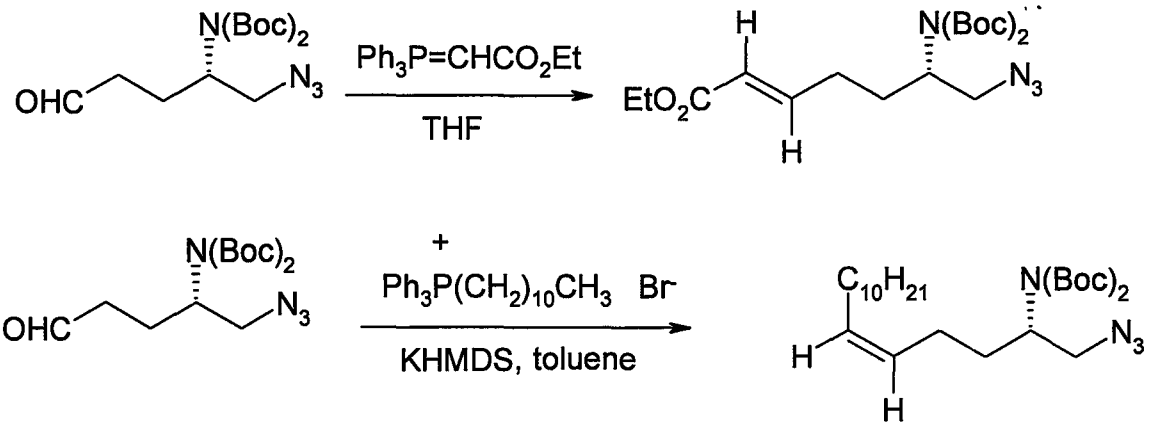
Equation 5. The Wittig coupling of Strobilurin G



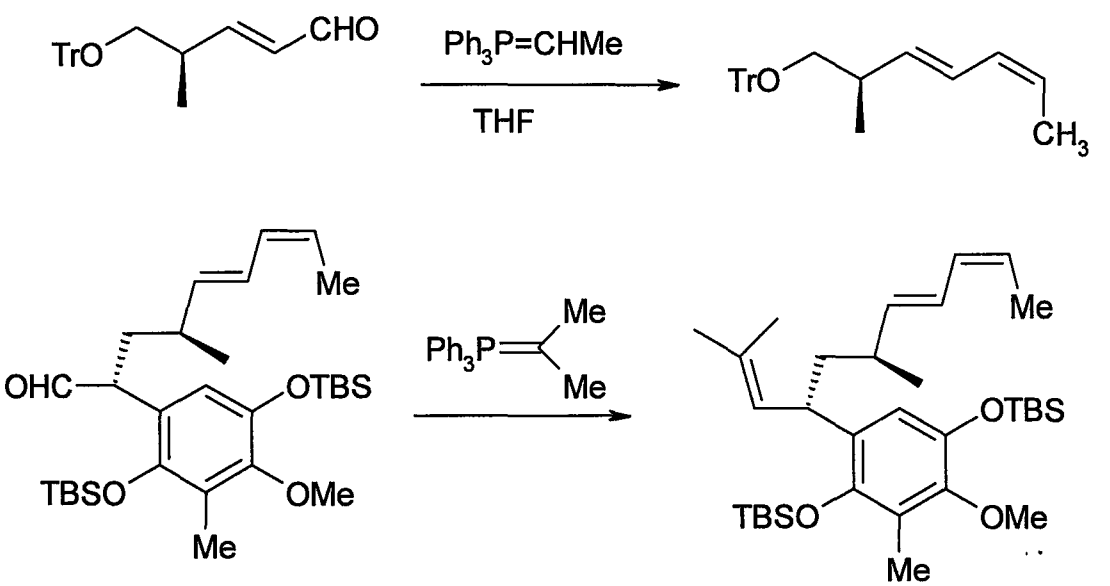
Steglich and coworkers had a *Z*-selective Wittig coupling as one of the key steps in their synthesis of Strobilurin G (Equation 5).[16] The ylide $Ph_3P=CBrCH_3$ was generated in situ, adding excess base to (1,1-dibromoethyl)triphenylphosphonium bromide.

The synthesis of chiral terminal 1,2-diamines (Equation 6) relied on a linkage of ylide and aldehyde. Kokotos[17] found that a stabilized ylide combined with an aldehyde resulted in *E* olefine in 80%. Treatment of aldehyde with nonstabilized ylide led to the *Z* product.

Equation 6. The Wittig olefination in the preparation of diamines



Equation 7. Two Wittig reactions in the synthesis of Elisabethin A



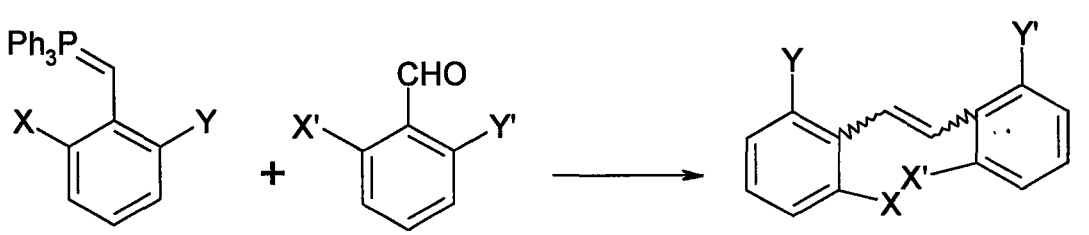
In the total synthesis of Elisabethin A (Equation 7), [18] Mulzer performed two Wittig reactions. The *Z*-geometry was installed by a lithium-salt-free condition (NaHMDS, Ph_3PEtBr) to give isomerically pure diene. A high yield (95%) of olefin was obtained in the reaction of aldehyde with $Ph_3P=C(CH_3)CH_3$.

1.4. Problems and modifications of the Wittig reactrion

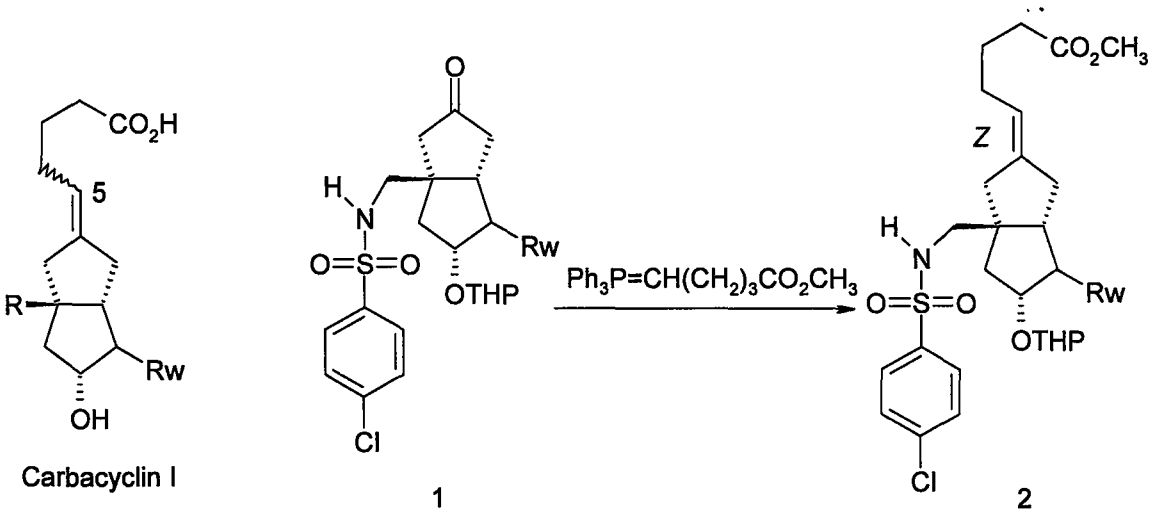
There have been two major ubiquitous problems in the Wittig olefination including the lack of steroselectivity in the reaction and the difficulty of removing triphenylphosphine oxide from the product.[6]

Many biologically active compounds (vitamins, lipids, pheromones etc) require the reliable synthesis of an olefin with a defined geometry. Schlosser's "leeward" approach model,[9 (a)] Vedejs' rationale of a four-center asynchronously-formed transition state,[12] and the subsequent work of Maryanoff[19] provided possible solutions to solve the *E*/*Z* selectivity. Schlosser[9 (a)] proposed that a 1,3–interaction in the transition state, leading to the planar oxaphosphetane, was the key to the cis geometry of the oxaphosphetane. However, the work of Maryanoff[19] and Vedejs[12] implied that the oxaphosphetane ring was not necessarily planar. Vedejs' model[12] (Scheme 3) offers a useful tool for *E*/*Z* selectivity. Gilheany[20] employed this model to synthesize predictably *E* or *Z* isomer stilbenes (Equation 8). Gilheany found there was a co-operative effect of one *ortho*-halo group on each of the two reacting partners that increases *Z*-selectivity, however two halo groups on the same reactants gives high *E*-selectivity.

Equation 8. Co-operative *ortho*-effects on the Wittig reaction



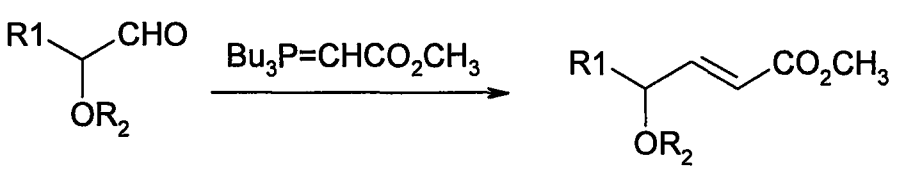
Equation 9. *Z*-selectivity induced by the interaction of charges



In the course of synthesis of carbacyclin I[21] (Equation 9), an α-chain was normally introduced in an unselective manner by the Wittig reaction, leading to *E*/*Z* =1 isomers at position 5. However, the Wittig reaction of 1 with ylide proceeded in a high *Z*-selectivity. This result might be explained by an intermolecular interaction of the charges at the deprotonated sulfonamide and phosphorous prior to the stereoselective C-C bond forming step, leading to the formation of a cis intermediate.

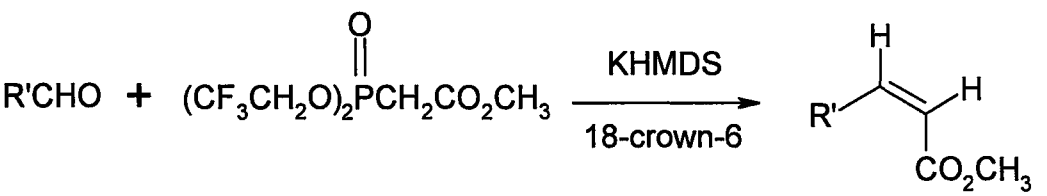
Recently, Martin's group[22] improved the *E*-selectivity in the Wittig reaction using tributylphosphorane ylide rather than triphenylphosphorane ylide, to give the *E*-α, β-unsaturated esters (Equation 10). Replacing the aryl rings on the phosphorus atom of stabilized ylides with alkyl groups could lead to increased *E*-selectivity in the reaction of α-alkoxyaldehydes with ylides.

Equation 10. *E*-selectivity olefination using tributylphosphorane ylide



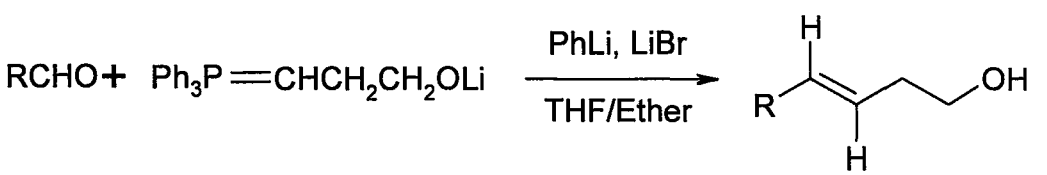
It is well known that the Wittig reaction of aldehydes with stabilized ylides gives the *E*-olefins as a major product (Horner-Wadsworth-Emmons reaction) and nonstabilized ylides react with aldehydes to form largely *Z* alkenes.[6 (d)] However, Still and Gennari[23] found that *Z*-unsaturated esters could be prepared by a Horner-Wadsworth-Emmons reaction using bis(trifluoroethyl)phosphonoester, KHMDS and 18-crown-6 (Equation 11). Mild and weakly basic systems have minimally complex counter irons. Therefore, they facilitate elimination and thus maintain high *Z* stereoselection.

Equation 11. Still modification



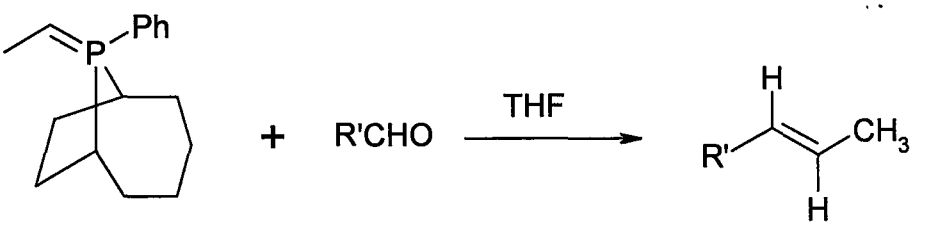
Schlosser modified the Wittig reaction with nonstabilized ylides to allow for the synthesis of *E*-olefins (Equation 12).[24] An over-stoichiometric concentration of the strong base (phenyllithium) and lithium bromide was required to obtain the product with high *E*-selectivity. It involved the formation of betain ylide.

Equation 12. Schlosser modification



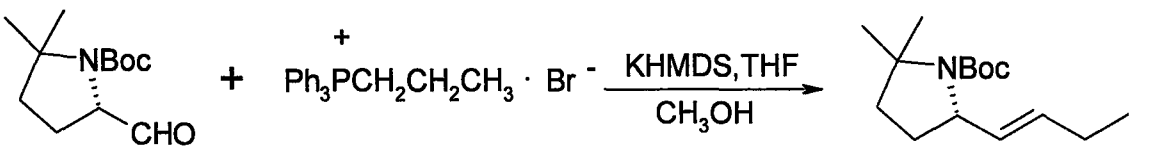
Vedejs[25] described that the bridged tetrahydrophosphole ylide (nonstabilized ylide) reacted with aldehydes to yield the *E*-alkanes (Equation 13). Its transition state minimized 1,3-interactions.

Equation 13. *E*- selective Wittig reactions with a bridged tetrahydrophosphole ylide



Recently, Kim[26] reported the high *E*-selectivity in the Wittig olefination of Garner's aldehyde with a nonstabilized ylide by quenching the reactions with an excess of CH_3OH at –78 °C (Equation 14). Excess of alcohol is necessary to shift the oxaphosphetane intermediate to the β-hydroxyphosphonium methoxide salt.

Equation 14. *E*- selective Wittig reactions with nonstablized ylides



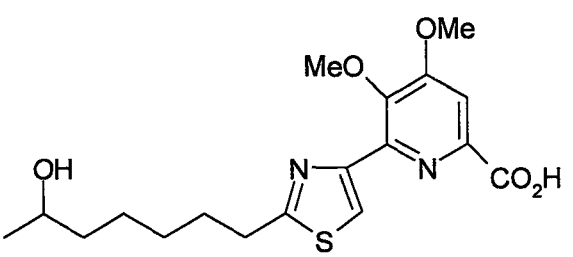
The Wittig reaction relies on the readily available triphenylphosphonium ylides. Triphenylphosphine oxide removal represents a major problem in the industrial synthesis of various bioactive compounds. Because triphenylphosphine oxide is difficult to separate from the products, separation methods have been investigated. Trippett[27] formed ylides from P-dimethylaminophenyldiphenylphosphine, therefore permitting acid extraction to be used to remove the oxide. Daniel[28] replaced one of the phenyl groups with 2-carboxyethyl group, thereby allowing base extraction to remove the oxide.

Based upon these studies, a new strategy for the Wittig reaction has been developed and presented herein. This alternative process is based on the use of stabilized or semistabilized trialkylphosphonium ylides with aldehydes to obtain high stereoselective olifines and facilitate the workup.

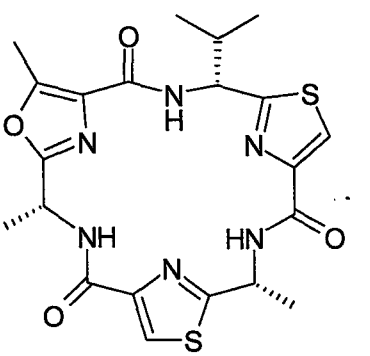
1.5. Natural products containing thiazole groups

Many natural products that possess thiazole groups exhibit attractive biological activities. Figure 1 shows some natural products containing thiazole groups. WS75624 B[29] was isolated from the fermentation broth of *Saccharothrix* sp. It is a potential endothelin converting enzyme inhibitor and antihypertensive agent. Dendroamide A,[30] which has two thiazole groups, demonstrated significant activity against tumors. Lyngbyabellin A[31] exhibits cytotoxic properties against human cancer cell lines and is a potent disruptor of the cellular microfilament network. Epothilone D[32] is of current clinical interest as an antitumor medicine.

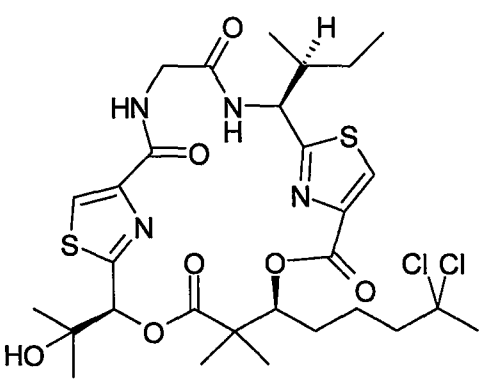
Figure 1. Some natural products containing thiazole groups



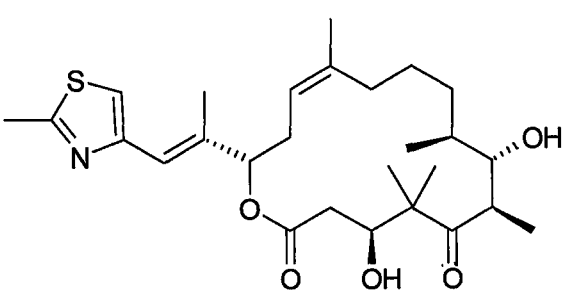
WS75624 B



Dendroamide A



Lyngbyabellin A



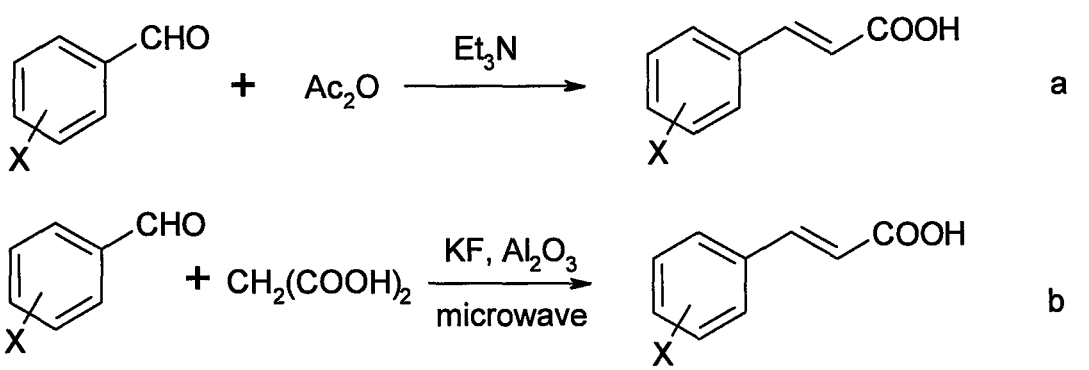
Epothilone D

In this thesis, the thiazole group is introduced into the target molecules via the Wittig reaction.

1.6. Preparations of cinnamic acid and α, β-unsaturated aldehydes

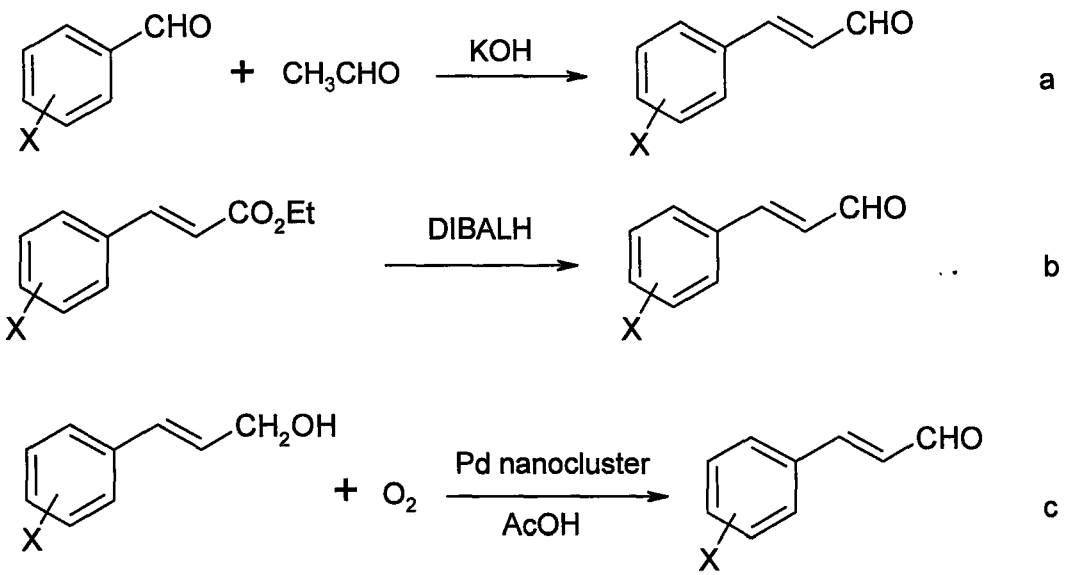
Cinnamic acid and its analogues are of practical interest in the preparation of biological compounds.[33] The classic synthesis of cinnamic acid was employed by the Perking reaction in which benzylaldehyde reacted with acetic anhydride in the presence base (Scheme 4a).[34] Perez developed a new approach using benzylaldehyde and malonic acid under microwave irradiation on potassium fluoride and aluminum oxide (Scheme 4b).[35]

Scheme 4. Preparation of cinnamic acid



In the chemical industry, α, β-unsaturated aldehydes are the starting materials for the synthesis of foods and medicines.[36, 37] Aromatic α, β-unsaturated aldehydes can be prepared through the Perking reaction, in which an aromatic aldehyde reacted with acetaldehyde under basic conditions (Scheme 5a). [38 (a)] Reduction of α, β-unsaturated ester with DIBALH[38 (b)] resulted in corresponding aldehydes (Scheme 5b). Recently, Kaneda and coworkers[38 (c)] described the selective oxidation of cinnamyl alcohol to cinnamaldehyde in the presence of palladium nanocluster as a heterogeneous catalyst (Scheme 5c).

Scheme 5. Preparation of α, β-unsaturated aldehydes



1.7. The objectives of this thesis

1). In order to solve the problems of the Wittig reaction, stabilized and semi stabilized trialkylphosphorus ylides were used to obtain high stereoselective olefins.

2). New approached to the synthesis of cinnamic acid and *α*, *β*-unsaturated aldehydes were proposed. *α*, *β*-unsaturated aldehydes were synthesized through olefination of an acetal-ylide, followed by hydrolysis and cinnamic acid was prepared via Wittig olefination of dimethylmalonyltributylphosphorane followed by hydrolysis and decarboxylation.

Chapter 2

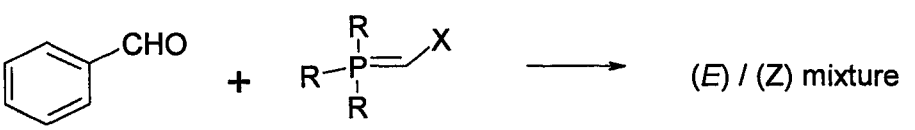
Results and Discussion

The stereochemistry of the Wittig reaction for the olefination of aldehydes with phosphorus ylides is strongly dependent on the type of ylide and the exact reaction conditions (Scheme 6). The olefination reaction of α-alkoxyaldehydes with stabilized ylides (tributylphosphorane) was found to proceed smoothly to give *E*-α, β-unsaturated esters in high yields.[22] However, there are two problems in the synthesis of olefins: the lack of *E*/*Z* selectivity and the difficulty of removing triphenylphosphine oxide.

Scheme 6. Stereochemistry of the Wittig reaction

1) Aliphatic aldehyde + aliphatic triphenylphosphonium ylide ⟶ (*Z*)-olefin
(unstabilized ylide)

2) Aromatic aldehydes and non stabilized (X=alkyl) or stabilized (X=CO_2Et, vinyl etc) ylides give (*E*) predominantly or mixtures through intermediate isomerization.



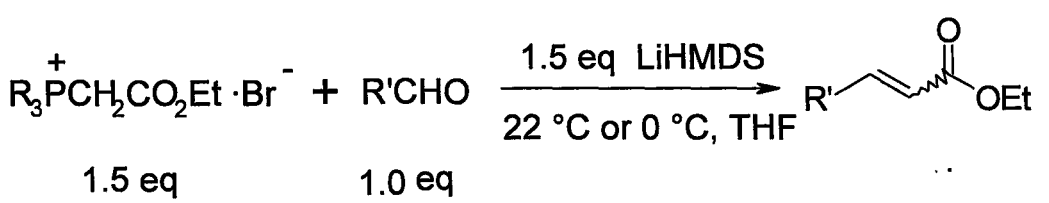
The hypothesis of this thesis is to use alkyl groups on phosphorus (R=Et, Bu, i-Bu etc) with various X to obtain high stereoselective olefins as a route to biologically active compounds (vitamins, lipids, flavonoids, pheromones etc). In addition, it is well known that trialkylphosphine oxides are water soluble. We can resolve the second problem by using trialkylphosphorus ylides.

In order to overcome the problems of the Wittig reaction, we have conducted a systematic study using structurally different ester or allylic trialkylphosphorus ylides with aldehydes (Equation 11-12). Furthermore, since many natural products that contain

thiazole group have biological activities, the thiazole group was introduced into the target molecules (Table 5).

2.1. Wittig Olefination reaction of ester trialkylphosphorus ylides.

The results of the reactions of ester phosphonium salts with aromatic aldehydes under LiHMDS are summarized in Table 1. The phosphonium salt was treated with LiHMDS at 22 °C or 0 °C in THF to generate the ylide, which was allowed to react with an aldehyde at 22 °C or 0 °C. It was observed that the *E*-selectivities and yields in the olefination at 22 °C (Table 1, entries 2, 4) were higher than those at 0 °C (Table 1, entries 1, 3). Therefore, subsequent reactions were carried out at 22 °C as the standard condition.

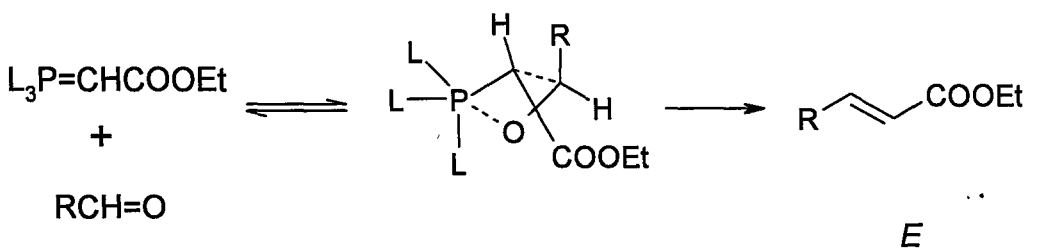


Equation 15. Olefination of aldehydes with ester phosphorus ylides

Under the same conditions, with the same aromatic aldehydes, the yields and *E*/*Z* ratios in ethoxycarbonyl ylides (Table 1, entries 2, 4-14) exhibited the following trend: $Et_3P^+CH_2CO_2Et•Br^-$>$(n\text{-}Bu)_3P^+CH_2CO_2Et•Br^-$>$(i\text{-}Bu)_3P^+CH_2CO_2Et•Br$>$Ph_3P^+CH_2CO_2Et•Br^-$. However, with the same aliphatic aldehydes, the trend (Table 2, entries 1-12) was: $(i\text{-}Bu)_3P^+CH_2CO_2Et•Br^-$>$Et_3P^+CH_2CO_2Et•Br^-$>$(n\text{-}Bu)_3P^+CH_2CO_2Et•Br$ >$Ph_3P^+CH_2CO_2Et•Br^-$. Generally, trialkylphosphonium salts give olefins with higher *E*/*Z* and yields than triphenylphosphonium salts. This result is in agreement with the increased basicity and nucleophilicity of the trialkylphosphorus ylides.[39] Among the trialkylphosphonium salts tested, $Et_3P^+CH_2CO_2Et•Br^-$ seems to be the best choice for

obtaining high *E*-selectivities and yields. With each phosphonium salt, the yields and *E*/*Z* ratios in the aromatic aldehydes (Table 1, entries 2, 4-14) show the following trend: p-anisaldehyde > benzaldehyde >4-nitrobenzaldehyde. Because of the stronger electron-releasing effect of 4-methoxyphenyl group, p-anisaldehyde with ylide produces an oxaphosphetane with a more stable phosphorus-oxygen bond.

Scheme 7. Mechanism of *E*-selectivity in ester ylides



From Table 1 and Table 2, it is noted that the reaction of ester stabilized ylides with aldehydes resulted in mainly *E*-alkenes, regardless of the type of ligand on the phosphine. In the slow step, ester-stabilized ylides attack the aldehyde to produce an oxaphosphetane for which the transition state favours a more stable planar state with a trigonal bipyramidal phosphorus, due to the decrease of the 1,3-interaction between the R and the ligand L (Scheme 7). Therefore, it leads to *E*-selectivities.

Table 1. Wittig Olefination reaction of aromatic aldehydes with ester phosphorus ylides

Entry	$R_3\overset{+}{P}CH_2CO_2Et \cdot Br^-$	Aldehyde	Product	Isolated yield %	*E/Z* %
1*	Ph	p-Anisaldehyde	A	77	93/7
2	Ph	p-Anisaldehyde	A	92	96/4
3*	n-Bu	p-Anisaldehyde	A	62	95/5
4	n-Bu	p-Anisaldehyde	A	98	98/2
5	i-Bu	p-Anisaldehyde	A	89	95/5
6	Et	p-Anisaldehyde	A	99	98/2
7	Ph	PhCHO	B	68	95/5
8	n-Bu	PhCHO	B	87	96/4
9	i-Bu	PhCHO	B	78	96/4
10	Et	PhCHO	B	95	98/2
11	Ph	4-nitrobenzaldehyde	C	76	93/7
12	n-Bu	4-nitrobenzaldehyde	C	78	94/6
13	i-Bu	4-nitrobenzaldehyde	C	88	94/6
14	Et	4-nitrobenzlaldehyde	C	87	100/0

*Entry 1, 3 at 0 °C, Others at 22 °C. *E/Z* ratios of the crude product were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). All yields are of the pure *E/Z* isomers.

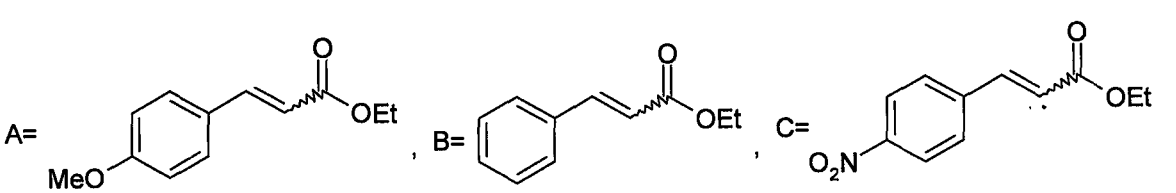
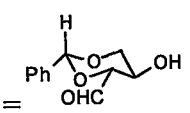
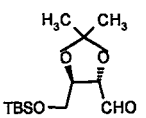
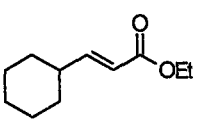


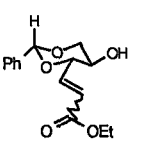
Table 2. Wittig Olefination reaction of aliphatic aldehydes with ester phosphorus ylides

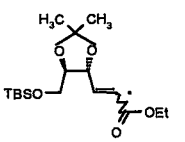
Entry	$R_3\overset{+}{P}CH_2CO_2Et \cdot Br^-$	Aldehyde	Product	Isolated yield %	*E*/*Z* %
1	Ph	cyclohexanecarboxaldehyde	D	71	100/0
2	n-Bu	cyclohexanecarboxaldehyde	D	74	100/0
3	i-Bu	cyclohexanecarboxaldehyde	D	97	100/0
4	Et	cyclohexanecarboxaldehyde	D	86	100/0
5	Ph	1	E	56	80/20
6	n-Bu	1	E	84	93/7
7	i-Bu	1	E	92	92/8
8	Et	1	E	91	100/0
9	Ph	2	F	62	58/42
10	n-Bu	2	F	77	96/4
11	i-Bu	2	F	83	94/6
12	Et	2	F	82	95/5

1= 

, 2= 

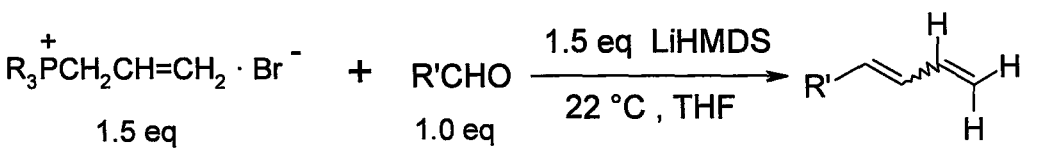
,D= 

, E= 

, F= 

2.2. Wittig Olefination reaction of allylic trialkylphosphorus ylides.

We report the Wittig olefination of several aldehydes with semistabilized allylic phosphorus ylides in Table 3 and Table 4. The formation of ylides was achieved through the addition of LiHMDS to the appropriate allylic phosphonium salt at 22 °C. The aldehyde of interest was then combined with the ylide at 22 °C and stirred overnight to



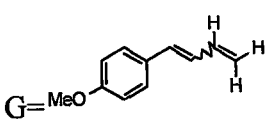
Equation 16. Olefination of aldehydes with allylic phosphorus ylide

produce an olefin. It is clear that in the allylic phosphonium bromides, $Et_3P^+CH_2CH{=}CH_2{\bullet}Br^-$ obtained higher yields and *E*/*Z* ratios than its phenyl analogue. The i-Bu and n-Bu analogues did not yield the olefin (Table 3 and Table 4).

The reaction mechanism with semistabilized phosphorus ylides is less understood because no direct evidence of the existence of oxaphosphetane intermediates from the ylides and aldehydes has been offered to date. However, Vedejs' rationale (Scheme 8) helps us to understand the stereochemical results with semistabilized allylic ylides. Under LiHMDS, the reaction of the triphenylphosphorus allylic ylides with benzyldehyde or p-anisaldehyde showed considerable kinetic *cis* selectivity for oxaphosphetane formation, mainly due to steric reasons, leading to the predominant formation of *Z* olefins (Table 3, entry 1, 5). A puckered four-center transition state (A) must dominate over a planar one (B) in an early transition state so as to avoid the 1,3-steric interaction between R^2 and L (L=Ph) (Scheme 8).

Table 3. Wittig Olefination reaction of aromatic aldehydes with allylic phosphorus ylides

Entry	$R_3\overset{+}{P}CH_2CH{=}CH_2 \cdot Br^-$	Aldehyde	Product	Isolated yield %	*E/Z* %
1	Ph	p-Anisaldehyde	G	58	42/58
2	n-Bu	p-Anisaldehyde	G	0	NR
3	i-Bu	p-Anisaldehyde	G	0	NR
4	Et	p-Anisaldehyde	G	63	74/36
5	Ph	PhCHO	H	43	39/61
6	n-Bu	PhCHO	H	0	NR
7	i-Bu	PhCHO	H	0	NR
8	Et	PhCHO	H	45	100/0
9	Ph	4-nitrobenzaldehyde	I	0	NR
10	n-Bu	4-nitrobenzaldehyde	I	0	NR
11	i-Bu	4-nitrobenzaldehyde	I	0	NR
12	Et	4-nitrobenzaldehyde	I	26	100/0

G= 

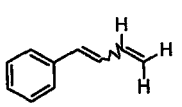
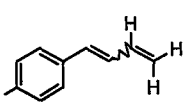
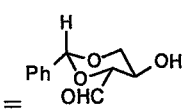
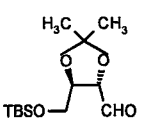
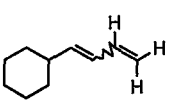
, H= 
, I= 

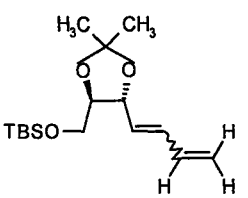
Table 4. Wittig Olefination reaction of aliphatic aldehydes with allylic phosphorus ylides

Entry	$R_3\overset{+}{P}CH_2CH=CH_2 \cdot Br^-$	Aldehyde	Product	Isolated yield %	*E/Z* %
1	Ph	cyclohexanecarboxaldehyde	J	33	58/42
2	n-Bu	cyclohexanecarboxaldehyde	J	0	NR
3	i-Bu	cyclohexanecarboxaldehyde	J	0	NR
4	Et	cyclohexanecarboxaldehyde	J	53	100/0
5	Ph	1	No product	0	NR
6	n-Bu	1	No product	0	NR
7	i-Bu	1	No product	0	NR
8	Et	1	No product	0	NR
9	Ph	2	K	0	NR
10	n-Bu	2	K	0	NR
11	i-Bu	2	K	0	NR
12	Et	2	K	42	100/0

1= 

, 2= 

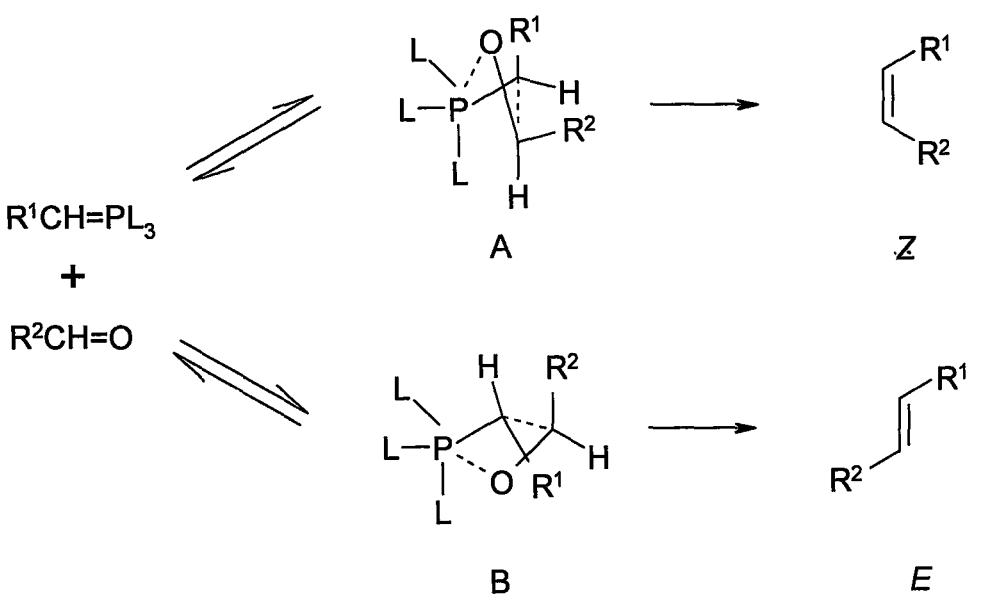
, J= 

, K= 

On the other hand, with cyclohexanecarboxaldehyde a 19% increase of *trans* selectivity was observed under the same conditions (Table 4, entry 1). This result indicates that a planar four-center transition state (B) is kinetically favoured even for triphenylphosphorus ylide, probably owing to the 1,2-steric interaction between R^1 and a

large R^2 (cyclohexyl group) (Scheme 8), together with the decreased 1,3-interaction between L (Ph) and the secondary alkyl group R^2. Generally, *trans* selectivity was observed in the lithium-containing reactions with triethylphosphorus ylides, giving predominant *E* olefins (Table 3, entries 4, 8, 12; Table 4, entries 4, 12). These reactions should favour a more stable planar transition state (B), probably due to the great decrease of the 1,3-interaction between R^2 and a compact L (ethyl). In the case of triethylphosphorus allylic ylides, because the steric demand of the ylide decreases, larger aldehydes (aromatic or aliphatic aldehydes) achieve high *E* selectivity. Thus, the degree of the 1,2-steric interaction between R^1 and R^2 in an early four-center transition state seems to induce the observed stereochemistry (Scheme 8). In the case of triphenylphosphorus allylic ylides, bulky R^2 groups, such as the aromatic group, favor the puckered transition state (A) due to the severe 1,3-steric interaction. This leads to the

Scheme 8. Vedejs' rationale for allylic ylides



predominant or exclusive formation of *Z* olefins even under the same conditions, while the large secondary alkyl group R^2, such as the cyclohexyl group, prefers the planar one

(B), owing to the 1,2-steric interaction and the decreased 1,3-interaction, to give *E* olefins predominantly under the base condition.

From Tables 1-4, it can be concluded that with the same aliphatic aldehydes, ethoxy carbonylethyl phosphonium bromides obtained higher yields and *E*/*Z* ratios than the corresponding allylic phosphonium bromides because the α proton in the ethoxy carbonylethyl phosphonium bromide is more acidic than that in the allylic phosphonium bromide. It follows that the ylide is more easily achieved in the case of ethoxy carbonylethyl phosphonium bromide.

Following the workup, TLC showed that no trialkylphosphine oxides were present in the organic layer, indicating that trialkylphosphine oxides were successfully separated from the olefin products. However, this was not the case for triphenylphosphine oxide, as TLC showed its presence within the organic layer.

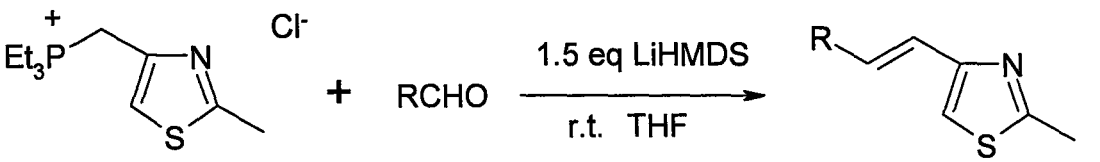
2.3. Wittig olefination reaction of thiazole triethylphosphorus ylide

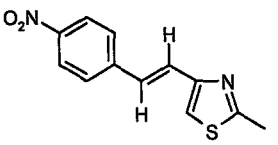
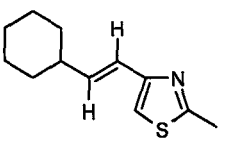
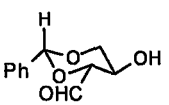
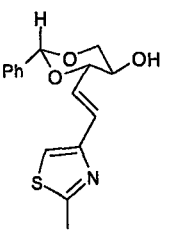
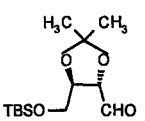
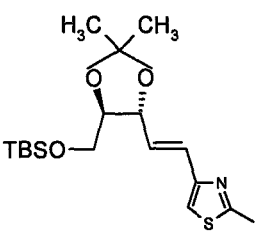
In the case of olefination reaction aldehydes with dimethyl thiazole ylide (semistabilized phosphorus ylide), Table 5 shows that among the aromatic aldehydes tested only 4-nitrobenzaldehyde reacted with thiazole ylide, obtaining pure *E* olefin product in a 41% yield (Table 5, entries 1-3). It is well known the carbonyl group in 4-nitrobenzaldehyde has very strong deficient electron effect. Therefore, it is susceptible to be attacked by the nucleophilic dimethyl thiazole ylide. Thiazole phosphonium chloride with aliphatic aldehydes (Table 5, entries 4-6), in the presence of LiHMDS, resulted in the products with higher yields and the *E* isomer exclusively. It can be explained that because the 1,3-interaction between the R and an ethyl group decreases, the degree of the

1,2-steric interaction between the R and thiazole group in the four-center transition state induce the observed *E*-stereochemistry (Scheme 9). This result coincides with the olefination of semistabilized allylic trialkylphosphorus ylides.

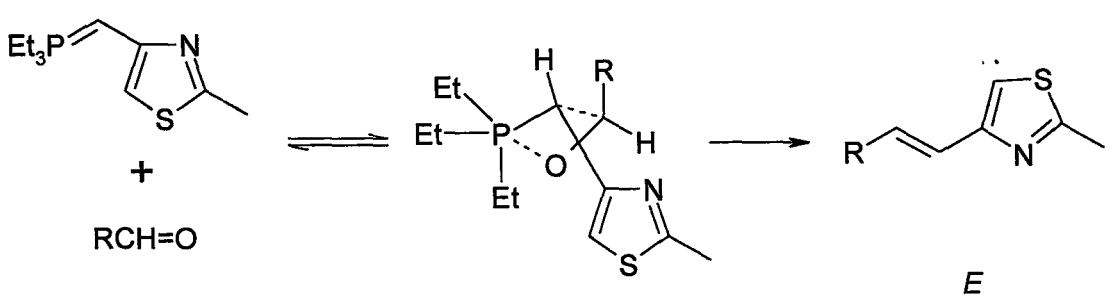
From Tables 1-5, with the identical phosphonium bromides, aliphatic aldehydes were found to be better than aromatic aldehydes in yields and *E*/*Z* ratios.

Table 5. Wittig olefination reaction of aldehydes with dimethyl thiazole ylide



Entry	Aldehyde	Product	Isolated yield, %	*E/Z*, %
1	p-Anisaldehyde	No Product	0	NR
2	PhCHO	No Product	0	NR
3	4-nitrobenzaldehyde		41	100/0
4	cyclohexanecarboxaldehyde		59	100/0
5			43	100/0
6			47	100/0

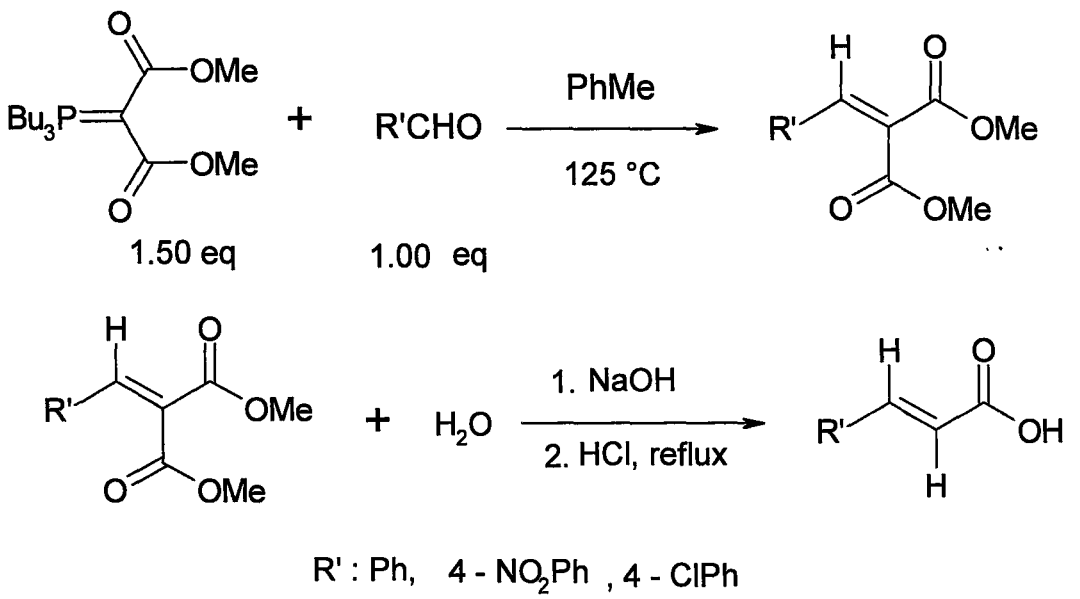
Scheme 9. Mechanism of *E*-selectivity in thiazole ylides



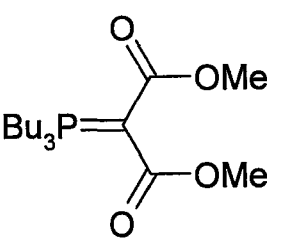
2.4. New approaches to cinnamic acid and α, β-unsaturated aldehydes

Cinnamic acid and analogues are of practical interest in the preparation of biological compounds.[33] We have investigated a new approach to cinnamic acids (Scheme 10).

Scheme 10. Synthesis of cinnamic acid



Dimethylmalonyltributylphosphorane (DMTP) is a new reagent that promotes the esterification reaction of chiral alcohols, allowing for the controlled inversion or retention of stereochemistry.[40]

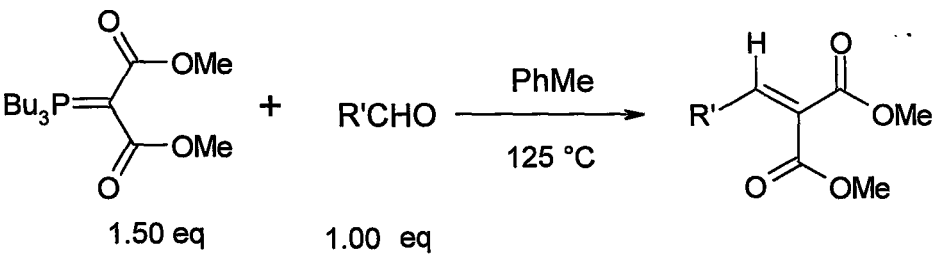


Dimethylmalonyltributylphosphorane (DMTP)

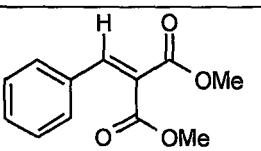
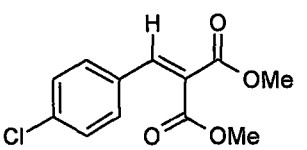
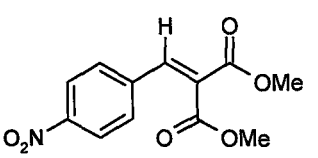
It is a colorless, viscous oil and stable under Argon at room temperature for at least 6 months. At the same time, DMTP is a stabilized ylide and should react with

aldehydes. We investigated the Wittig reaction of DMTP with aromatic aldehydes (Table 6)

Table 6. Wittig reaction of DMTP with aromatic aldehydes



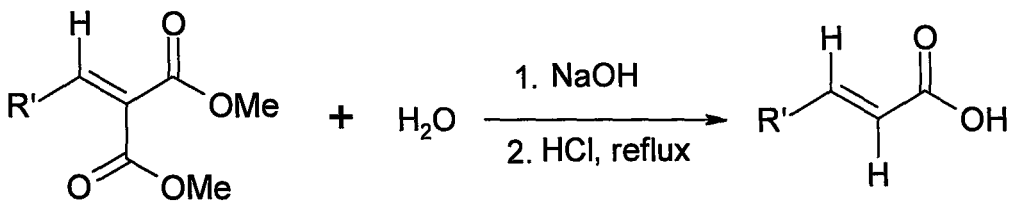
1.50 eq 1.00 eq

Entry	Aldehyde	Product	Isolated yield, %
1	PhCHO		14
2	4-chlorobenzaldehyde		31
3	4-nitrobenzaldehyde		81

The reactions reported in Table 6 were carried out in toluene at 125 °C for 48 hours. 4-Nitrobenzaldehyde gave the product in a much higher yield (87%, Table 6, entry 3), followed by 4-chlorobenzaldehyde (31%, Table 6, entry 2). Benzaldehyde only generated the olefin with a 14% yield (Table 6, entry 1). It is well known that the order of electron-withdrawing effect is: NO_2 > Cl > H. Because NO_2 has a strong electron-

withdrawing effect, the electron deficiency of the carbonyl group in 4-nitrobenzaldehyde is stronger than that in 4-chlorobenzaldehyde and benzaldehyde, causing 4-nitrobenzaldehyde to be more susceptible to be attacked by the nucleophilic ylide.

Table 7. Hydrolysis and decarboxylation of malonylate



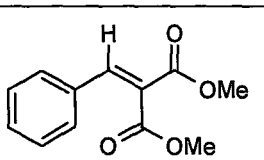
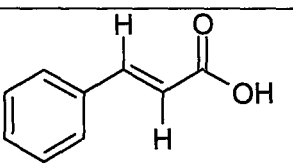
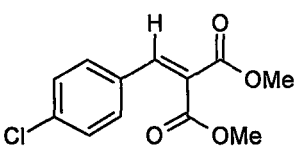
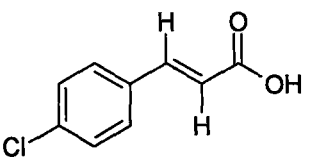
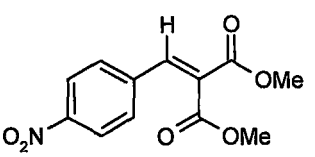
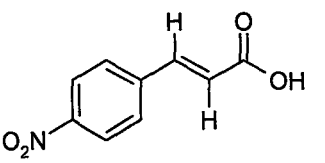
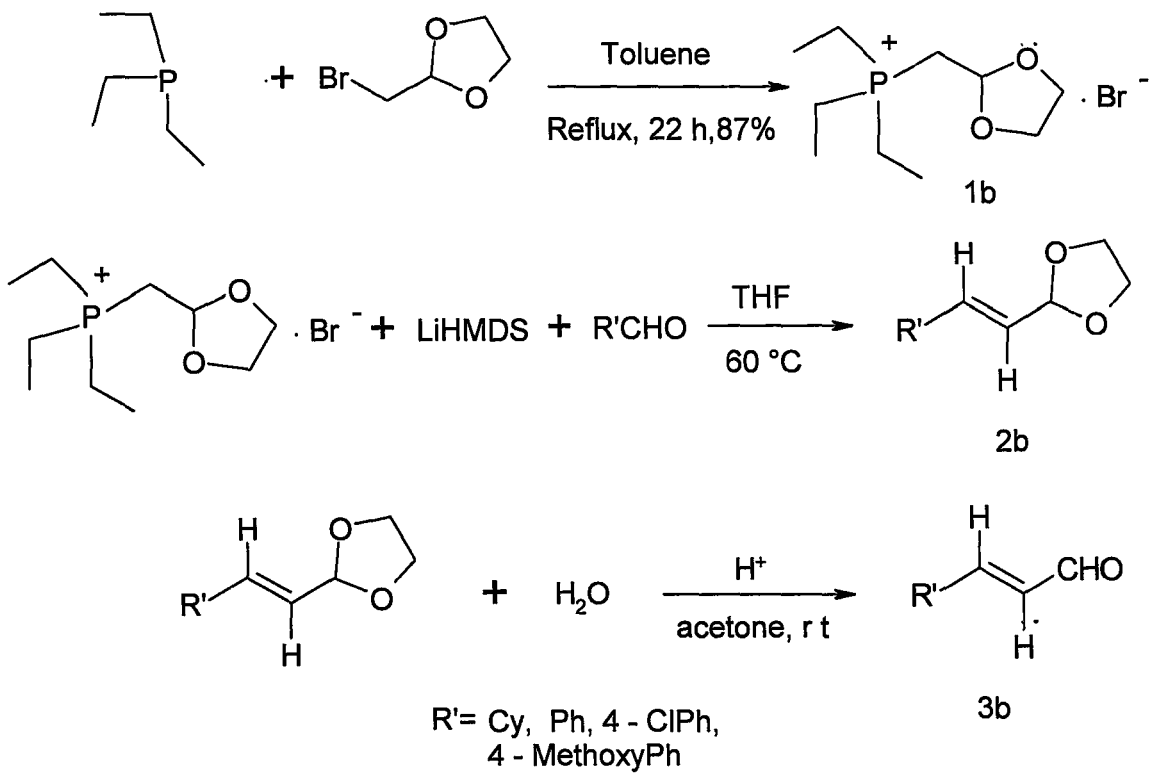
Entry	Malonylate	Product	Isolated yield, %
1			20
2			35
3			60

Table 7 summarizes the results of hydrolysis and decarboxylation of malonylate. 4-nitrocinnamic acid was obtained in a 60% yield (Table 7, entry 3). The two-step yield of 4-nitrocinnamic acid via the Wittig olefination was 48%. For 4-chlorocinnamic acid and cinnamic acid, the overall yields were 10% and 3%, respectively.

In the chemical industry, α, β-unsaturated aldehydes are largely used as starting materials and reagents for the synthesis of foods and medicines.[36, 37] We have investigated a new route to α, β-unsaturated aldehydes (Scheme 11).

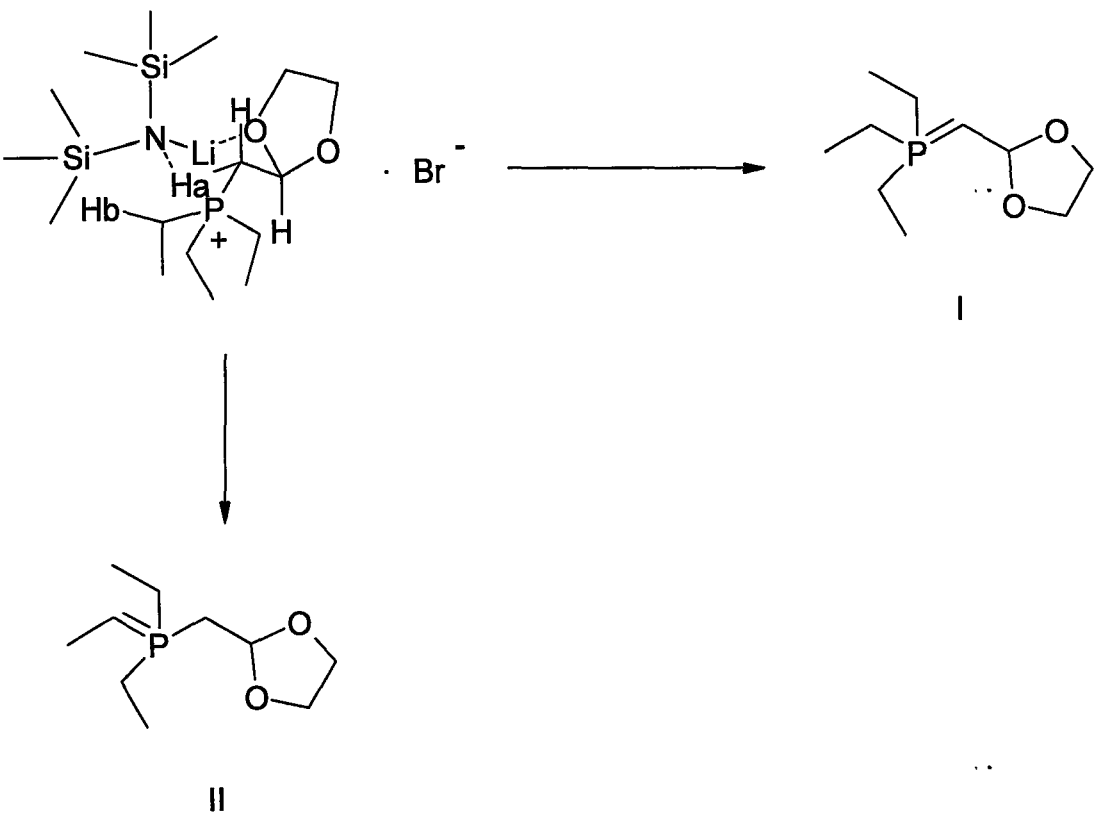
Scheme 11. Synthesis of α, β-unsaturated aldehydes



2'-(1, 3-dioxolanyl)-triethylphosphonium bromide 1b can be prepared in a good yield (87%), by the reaction of triethylphosphine with 2-bromomethyl-1, 3-dioxolane in toluene reflux for 22 hours. The phosphonium salt 1b was treated with LiHMDS to produce a ylide, which reacted with an aldehyde to afford an acetal olefin 2b. Finally, 2b was deprotected in water to give α, β-unsaturated aldehyde 3b. It should be emphasized that in the Wittig reaction, phosphonium salt 1b was eliminated under the base to generate two kinds of ylide: I and II (Scheme 11). Statistically, ylide I could be 75% (6 Hb) and ylide II could be 25% (2 Ha) of the final product. In fact, the ylide II is in the majority because the acetal olefins (Table 8) are mainly obtained. This can be explained

by both chelation and acidity involving a chelation controlled six-centered chair-like transition state as shown Scheme 12. Considering the stereoelectronic effect, the hydrogen Ha is easier to eliminate than Hb to form ylide II rather than ylide I (Scheme 12). The second reason is that Ha is more acidic than Hb, due to the acetal electron-withdrawing effect.

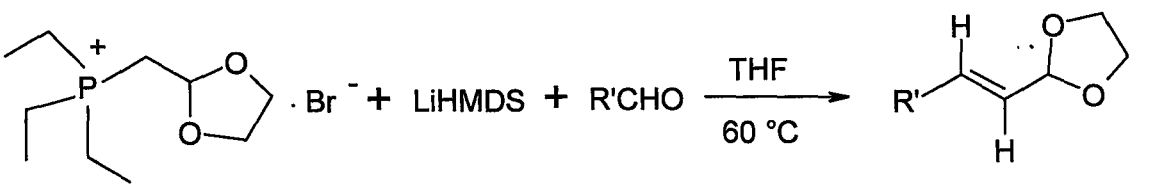
Scheme 12. Mechanism of ylide formation

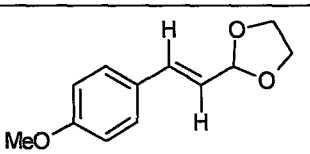
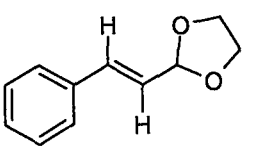
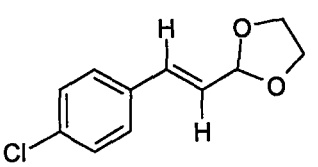
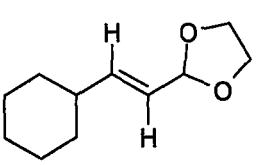


A series of experiments of aldehydes with phosphonium salt 1b in the presence of LiHMDS were conducted to examine the *E*-selectivity and yield. The results are summarized in Table 8. In all of the cases tested, pure *E*-olefines were obtained. 4-chlorobenzaldehyde resulted in the highest yield among the aldehydes (Table 8, entry 3). Benzaldehyde resulted in more product than p-anisaldehyde (Table 8, entries 1-2). Cyclohexanecarboxaldehyde resulted in the modest yield (Table 8, entry 4). Generally,

aromatic aldehydes (Table 8, entries 1-2) are more effective than aliphatic aldehydes (Table 8, entry 4) in this Wittig olefination reaction.

Table 8. Wittig reaction of aldehydes with 2'-(1, 3-dioxolanyl)-triethylphosphonium bromide

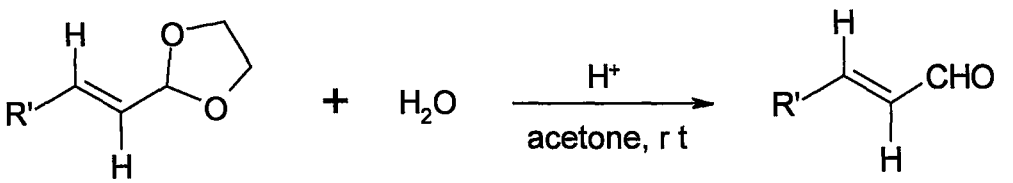


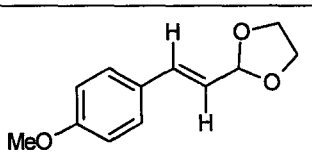
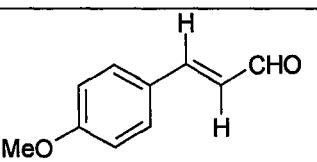
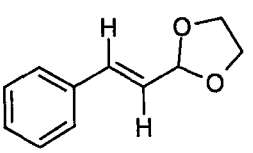
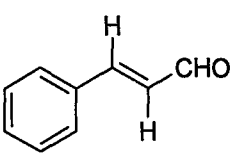
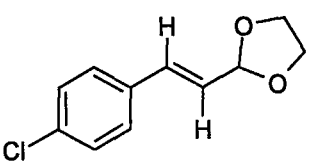
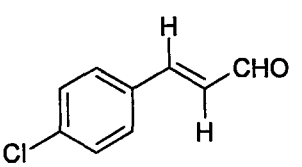
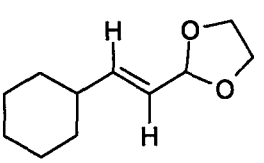
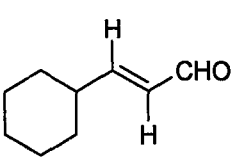
Entry	Aldehyde	Product	Isolated yield, %	*E/Z*, %
1	p-Anisaldehyde		62	100/0
2	PhCHO		72	100/0
3	4-chlorobenzaldehyde		76	100/0
4	cyclohexanecarboxaldehyde		32	100/0

Cinnamaldehyde, 4-methoxycinnamaldehyde and 3-cyclohexyl-2-(*E*)-allyl aldehyde

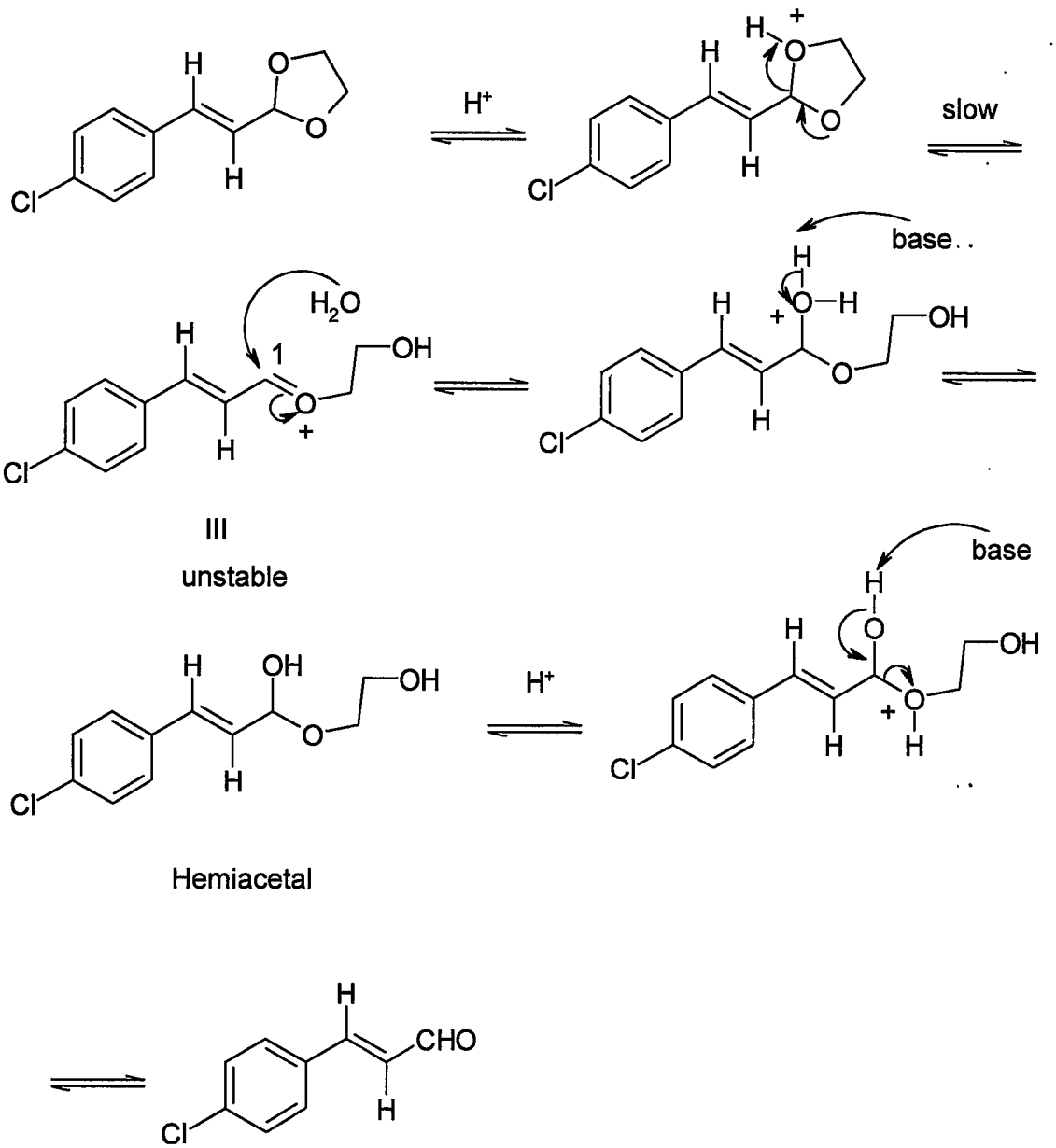
(Table 9, entries 1, 2, 4) can be easily prepared with corresponding acetals in a dilute acid at room temperature for 15 minutes. It was found that the hydrolysis of 2-[(*E*)-(4'-chloro)styryl]-(1,3)dioxolane could not proceed under a dilute acidic condition. Only in concentrated sulfuric acid at room temperature for 36 hours would it convert to 4-chlorocinnamaldehyde.

Table 9. Hydrolysis of acetal.



Entry	Acetal	Product	Isolated yield, %	*E*/*Z*, %
1			85	100/0
2			80	100/0
3			86	100/0
4			18	100/0

Scheme 13. Mechanism of hydrolysis of 2-[(*E*)-(4'-chloro)styryl]-(1,3)dioxolane



In the rate determining step of hydrolysis of 2-[(*E*)-(4'-chloro)styryl]-(1,3)dioxolane (Scheme 13, transition state III), the electron-withdrawing inductive effect and electron-donating resonance effect of chlorine oppose each other, but the former is somewhat

stronger than the latter. Therefore, the carbon at position 1 bears a partial positive charge. Due to the instability of the two adjacent partial positive charges (III, Scheme 13), the hydrolysis of 2-[(*E*)-(4'-chloro)styryl]-(1,3)dioxolane becomes slower and requires more concentrated acid.

2.5. Conclusion

We have developed a class of stabilized and semi-stabilized trialkylphosphorus ylides that allow for the olefins with high stereoselectivities and high yields. Among the ester stabilized trialkylphosphorus ylides, triethylphosphorus ylides give *E*-alkenes in more than 82% yield and with *E*>95%. The reaction of semistabilized allylic triethylphosphorus ylides with aromatic aldehydes resulted predominantly in *E* isomers of olefins. On the other hand, the selective formation of *Z* olefins was achieved by using allylic triphenylphosphorus ylides and aromatic aldehydes. In the case of olefination reactions of aldehydes with dimethyl thiazole ylide, it was shown that among the aromatic aldehydes only 4-nitrobenzaldehyde reacted with this ylide and provided the olefin in 41% yield (*E*/*Z*=100/0). The side products of the Wittig reaction using trialkylphosphorus ylides, trialkylphosphine oxides, were completely removed by an extraction protocol.

We have developed a protocol for transforming aldehydes to α, β-unsaturated acids and aldehydes in good yields and high *E*/*Z* selectivity via the Wittig reaction. The protocol involves the use of either dimethylmalonyltributylphosphorane (DMTP) or acetal-ylide. The hydrolysis and decarboxylation of the alkene malonates resulted in α, β-unsaturated acids. The hydrolysis of acetal olefins gave α, β-unsaturated aldehydes.

Chapter 3

Isolation and Purification of Flavonoids

3.1. Introduction

Staphylococcus is a gram-positive cocci, several species of which act as bacterial pathogens or commensal organisms in both humans and animals. They are classified based on coagulase activity. Coagulase positive strains are classified as *Staphylococcus aureus* (*S. aureus*). *S. aureus* infections are one of the most common causes of hospital-acquired infections, yet they are increasingly difficult to treat due to the rate at which the bacteria acquire antibiotic resistance.

When penicillin was introduced in the mid 1940s, *S. aureus* was almost 94% susceptible to this drug. Widespread resistance to penicillin developed in the 1950s, followed by resistance to semi-synthetic penicillins in the 1960s and 1970s. Now 90% of *Staphylococcus* strains are resistant to penicillin and penicillin-derived antibiotics. The next line of defense, methicillin, is increasingly becoming less effective. Between 1975 and 1991, the prevalence of methicillin-resistant strains of *S. aureus* increased 26%. Resistance to methicillin in *Staphylococcus aureus* is also often accompanied by multidrug resistance. The high prevalence of methicillin-resistant staphylococci led to the use of vancomycin. For these methicillin-resistant strains, vancomycin is the only effective drug for treatment. However, recently some strains of *S. aureus* have been reported with decreased susceptibility even to vancomycin. These resourceful strains

have mutated to cause a single change at the termini of the vancomycin-binding site on the bacterial cell-wall peptidoglycan.[41]

The emergence of vancomycin-resistant *S. aureus* would present a very important issue in antibiotic resistance and it could cause very serious problems to those susceptible persons. As *S. aureus* has acquired resistance to penicillin, and semi-synthetic penicillin derivatives, such as methicillin, vancomycin remains the only drug to which the microorganism is susceptible. The emergence of antibacterial resistant infections is likely to be costly and might allow for the re-emergence of eradicated diseases (such as tuberculosis) in new and more potent forms.

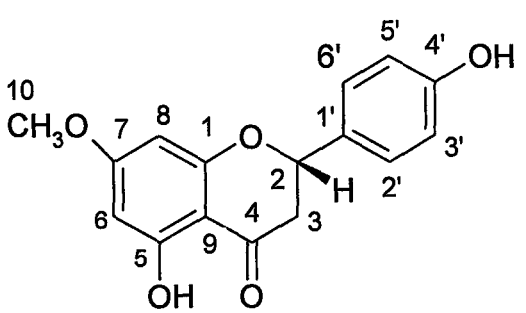
Given this threat, and the enormous financial toll that antibiotic resistant diseases have already taken on the health care system, finding new chemicals that are effective to vancomycin- and methicilin-resistant strains is very important. A comprehensive survey of natural products that exhibit anti-staphylococcal activity was reported earlier in 2004.[42] These include flavanoids, diterpenoids and alkaloids. This indicates that some of these may also show good activity against vancomycin-resistant strains of microbes.

3.2. Results and discussion

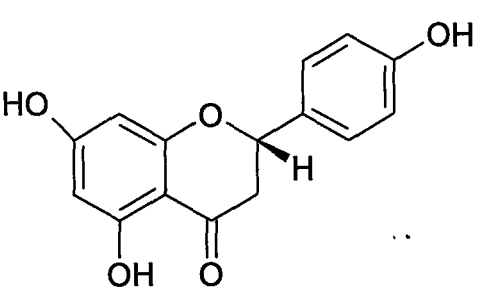
We observed a copious resinous excretion on diseased Prunus bark that appeared to be associated with a fungal growth. It was hypothesized that the plant resin may contain antifungal and/or antibacterial compounds in response to this pathogen and that these compounds may have cytostatic activity against other organisms of interest. A recent review[42] has shown that flavanoid-type compounds known to be present in *Prunus* bark

possess one of the most prevalent structural types observed amongst those exhibiting activity to multi-drug resistant strains of microbes.

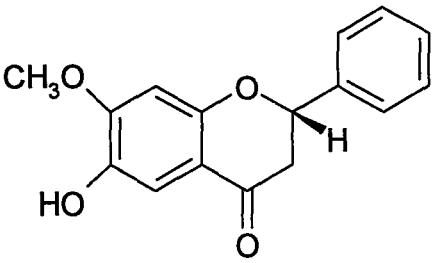
Cultivated *Prunus* species are widespread in North America and important economically in the fruit belt of Ontario. Resin from the bark of *Prunus sp* (62.2 g, dry weight, bark and resin) was collected (April 21st 2003) in St. Catharines, Ontario. The resin was associated with a lesion in one of the main branches of this approximately 75-year old tree. The area surrounding the lesion was covered with an unidentified fungus and lichen, however only the resin and bark was collected. This material was soaked in dichloromethane (225 mL) for one day, filtered and concentrated to give 425 mg of a semi-crystalline resin. The bark material was then soaked in methanol (100mL) for one day, filtered and the methanol solubles concentrated to give 1.45 g of dark brown oil containing some crystals. Analysis of the dichloromethane extract by TLC indicated the presence of polar UV active materials. The fraction (0.2095 g) was then subjected to silica gel column chromatography (hexanes/ethyl acetate=70/30) followed by a silica gel column (DCM), to separate Sakuranetin (0.0524 g, 25%, sample name: YHFR9), Naringenin (0.0177 g, 8.4%, sample name: YHFR21) and (2*S*)-7-methoxy-6-hydroxyflavanone (0.0290 g, 14.5%, sample name: YHFR17).



Sakuranetin



Naringenin



(2*S*)-7-methoxy-6-hydroxyflavanone

Sakuranetin has the molecular formular of $C_{16}H_{14}O_5$ as revealed by MS [m/z 286.0801(M^+)], IR absorptions at 3421(broad) and 1643 cm^{-1} indicating the presence of hydroxyl and carbonyl groups, respectively.[13]C-NMR (Table 10) disclosed the presence of a ketone. ^{1}H-NMR showed the AA'BB' system, characteristic of a 1, 4–disubstitued aromatic ring, and one signal attributed to one methoxyl group. The location of the methoxyl group at C7 of Sakuranetin, was easily deduced from an HMBC spectrum. HMBC revealed the connectivity of the C7 to a methoxyl group, C6 and C8. The arrangement of methoxyl group at C7 made H6 and H8 in the identical chemical environment. The correlation of H2 and H3 was derived from ^{1}H-^{1}H COSY. Thus, the structure can be depicted for Sakuranetin. Due to the hydrogen bond between the carbonyl in C4 and the hydroxyl group in C5, IR absorptions of carbonyl shifted to lower wavenumbers (1643 cm^{-1}) than normal. The spectral data agree with those published in the literature.[43, 44] The structures of Naringenin and (2*S*)-7-methoxy-6-hydroxyflavanone were also confirmed spectroscopically after isolation (experimental section). The biological testing of these compounds is in progress.

Table 10. NMR data for Sakuranetin in $CDCl_3$

Carbon Number	δ_C	δ_H(J, Hz)	HMBC	COSY
1	164.2		8	
1'	130.5		2	
2	79.1	5.35 (dd, 1H, J=13.2, 3.0 Hz)	1', 3	3
2'	128.0	6.88 (d, 2H, J=8.4 Hz)	1', 3'	6'
3	43.3	δ2.78 (dd, 1H, J=17.4, 3.0 Hz) 3.09 (dd, 1H, J=16.8, 13.2 Hz)	2, 4	2
3'	115.8	7.32 (d, 2H, J=8.4 Hz)	2'	
4	196.2		3	
4'	156.4			
5	163.0		6	
5'	115.8	7.32 (d, 2H, J=8.4 Hz)	6'	
6	95.2	6.05 (dd, 2H, J=15.1, 2.4 Hz)	5, 7	8
6'	128.0	6.88 (d, 2H, J=8.4 Hz)	5'	2'
7	168.1		6, 8, 10	
8	94.4	6.05 (dd, 2H, J=15.1, 2.4 Hz)	1,7	6
9	103.2			
10	55.8	3.80 (s, 3H)	7	
4'-OH				
5-OH		12.02 (s, 1H)		

Chapter 4

Experimental Section

4.1. General details

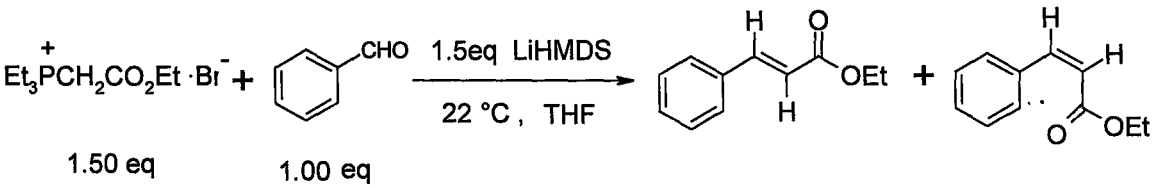
In the reactions described, all reagents were obtained from Aldrich except those noted below. All phosphonium salts were obtained from Cytec. Dry THF was obtained by disllation from a sodium-benzophenone mixture. Anhydrous toluene was obtained by distillation from sodium.

^{1}H-NMR spectra were recorded at 200 MHz and ^{13}C-NMR spectra were recorded at 50 MHz in $CDCl_3$ or CD_3OD on the Bruker Avance DPX-200 spectrophotometer. All 2-D NMR experiments were performed at 600 MHz in $CDCl_3$ or CD_3OD on the Bruker Avance DPX-600 spectrophotometer. MS analysis was performed on a High Resolution Micromass GCT mass spectrometer (EI/CI). FT-IR was recorded on a Mattson Research Series spectrophotometer using KBr plates. Melting points were determined on a melting point apparatus and were uncorrected.

4.2. General procedure for Wittig olefination reaction

4.2.1. Method A:

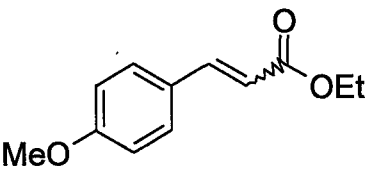
Ethyl cinnamate[45]



Into a dry round bottom flask was weighed ethoxy carbonyl ethyl triethyl phosphonium bromide (71.3 mg, 0.25 mmol, 1.5 equiv.) followed by dry THF (2.0 mL THF). At room temperature a solution of LiHMDS (0.25 mL, 0.25 mmol, 1.5 equiv.) was slowly injected via syringe over 5 minutes. The reaction mixture was then stirred at room temperature for 1 hour under argon. A solution of benzaldehyde (17 μL, 17 mg, 0.17 mmol, 1.0 equiv.) in 1mL THF was added in 3 minutes at room temperature. The mixture was stirred overnight under argon. An aqueous/organic (H_2O/CH_2Cl_2) workup was performed. The organic layer was washed three times and dried with Na_2SO_4. The solution was filtered by gravity through cotton and Na_2SO_4 then was washed with CH_2Cl_2 (3×4mL). The solvent was removed under reduced pressure to afford the crude product as oil. The crude product was purified on a silica gel column (hexane:ethyl acetate=80:20) providing ethyl cinnamate (28 mg, 95%, *E*:*Z*=98:2) as colorless oil.

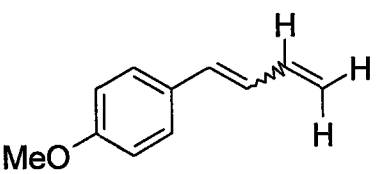
R_f=0.75 (silica, hexane:ethyl acetate=80:20)
^{1}H-NMR ($CDCl_3$): δ 1.09 (t, 3H, J=7.0 Hz), 4.12 (q, 2H, J=7.3 Hz), 6.29 (d, 1H, J=17.2 Hz), 7.21-7.51 (m, 5H), 7.60 (d, 1H, J=17.6 Hz)
^{13}C-NMR ($CDCl_3$): δ167.40, 144.97, 134.83, 130.61, 129.26, 128.43, 118.64, 60.90, 14.72
MS: *m/z*: 177, 176, 162, 161, 131, 130, 103, 44
FT-IR: 2981, 1711, 1638, 1495, 1449, 1311, 1202, 1095, 1038, 980, 768, 712, 685 cm^{-1}
High Resolution Mass Spectrum for $C_{11}H_{12}O_2$, calcd *m/z* 176.0837, found 176.0837

(*E*) or (*Z*)-ethyl 4-methoxycinnamate[45]



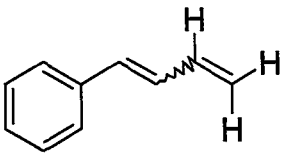
White oil
R_f=0.70 (silica, hexane:ethyl acetate=80:20)
^{1}H-NMR ($CDCl_3$): δ 1.25 (t, 3H, J=7.0 Hz), 3.74 (s, 3H), 4.16 (q, 2H, J=7.0 Hz), 6.52 (d, 1H, J=15.7 Hz), 6.82 (d, 2H, J=8.6 Hz), 7.38 (d, 2H, J=8.7 Hz), 7.82 (d, 1H, J=15.8 Hz)
^{13}C-NMR ($CDCl_3$): δ 167.73, 161.69, 144.63, 130.07, 127.55, 116.10, 114.68, 60.71, 55.74, 14.75
MS: *m/z*: 207, 206, 178, 161, 135, 134, 107, 92, 77
FT-IR: 3012, 2980, 2906, 2838, 1709, 1634, 1605, 1513, 1423, 1367, 1289, 1254, 1204, 1171, 1111, 1032, 984, 829 cm^{-1}
High Resolution Mass Spectrum for $C_{12}H_{14}O_3$, calcd *m/z* 207.0976, found 207.0985

(*E*) or (*Z*)-1-(4'-methoxyphenyl)-1,3-butadiene[46]



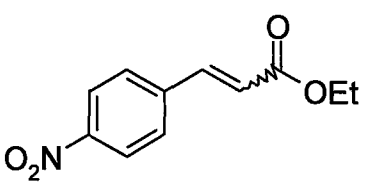
Colorless oil
R_f=0.80 (silica, hexane:ethyl acetate=70:30)
^{1}H-NMR ($CDCl_3$): δ 3.67 (s, 3H), 4.97 (dd, 1H, J=9.8, 1.7 Hz), 5.06 (dd, 1H, J=16.2, 1.8 Hz), 6.12 (dd, 1H, J=16.1, 9.8 Hz), 6.35 (dd, 1H, J=16.7, 10.0 Hz), 6.52 (dd, 1H, J=16.6, 2.5Hz), 6.79 (d, 2H, J=7.0 Hz), 7.13 (d, 2H, J=7.2 Hz)
^{13}C-NMR ($CDCl_3$): δ 161.84, 144.20, 139.22, 136.9(d), 134.47, 125.81, 123.30, 120.88 (d), 62.11
MS: *m/z*: 161, 136, 131, 119, 107, 85, 83, 77, 48
FT-IR: 2934, 2837, 1669, 1601, 1512, 1462, 1424, 1304, 1251, 1175,1030, 973, 830 cm^{-1}
High Resolution Mass Spectrum for $C_{11}H_{12}O$ calcd *m/z* 160.0888, found 161.0599

(*E*) or (*Z*)-1- phenyl-1, 3-butadiene[47]



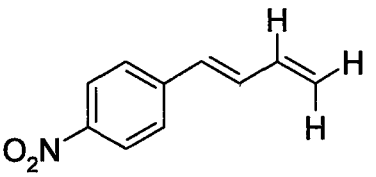
Colorless oil
R_f=0.85 (silica, hexane:ethyl acetate=70:30)
^{1}H-NMR ($CDCl_3$): δ 5.02 (dd, 1H, J=9.9, 1.9 Hz), 5.15 (dd, 1H, J=16.7, 1.8 Hz), 6.38 (dd, 1H, J=16.8, 9.8 Hz), 6.59 (dd, 1H, J=16.7, 9.8 Hz), 6.76 (dd, 1H, J=16.6, 2.0 Hz), 7.07-7.24 (m, 5H)
^{13}C-NMR ($CDCl_3$): δ 143.98, 139.25(d), 137.59, 136.20(d), 135.61(d), 134.45, 133.86, 124.48
MS: *m/z*: 133, 131, 130, 129, 105, 91, 77, 43
High Resolution Mass Spectrum for $C_{10}H_{10}$ calcd *m/z* 130.0782, found 130.0474

(*E*) or (*Z*)-ethyl 4-nitrocinnamate[48, 45 (b)]



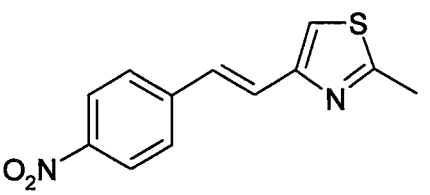
Yellow oil
R_f=0.65 (silica, hexane:ethyl acetate=80:20)
E: ^{1}H-NMR ($CDCl_3$): δ 1.28 (t, 3H, J=5.6 Hz), 4.20 (q, 2H, J=5.5 Hz), 6.48 (d, 1H, J=15.9 Hz), 7.58-7.66 (m, 4H), 8.17 (d, 1H, J=16.0 Hz)
^{13}C-NMR ($CDCl_3$): δ 166.42, 141.99, 140.96, 129.00, 124.56, 123.57, 122.96, 61.40, 14.65
MS: *m/z*: 222, 221, 193, 176, 146, 130, 102, 76, 75
FT-IR: 2995, 1718, 1648, 1595, 1519, 1346, 1190, 1109, 1027, 979, 858, 845, 758 cm^{-1}
High Resolution Mass Spectrum for $C_{11}H_{11}NO_4$ calcd *m/z* 221.0688, found 221.0693

(*E*)-1-(4'-nitro)-phenyl-1, 3-butadiene



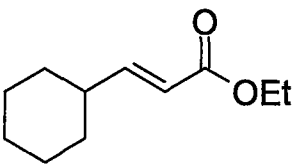
Yellow oil
R_f=0.60 (silica, hexane:ethyl acetate=70:30)
^{1}H-NMR ($CDCl_3$): δ 5.28 (dd, 1H, J=16.5, 2.4 Hz), 5.36 (dd, 1H, J=16.0, 2.3 Hz), 5.42 (dd, 1H, J=16.1, 2.3 Hz), 6.50 (dd, 1H, J=16.0, 2.2 Hz), 6.90 (dd, 1H, J=12.3, 2.5 Hz), 7.50 (d, 2H, J=6.8 Hz), 8.18 (d, 2H, J=6.6 Hz)
^{13}C-NMR ($CDCl_3$): δ 150.46, 143.21, 140.79, 137.01(d), 134.72, 133.61(d), 130.61(d), 127.78
MS: *m/z*: 176, 175, 164, 158, 129, 128, 127, 83, 77, 48
FT-IR: 2924, 2853, 1677, 1597, 1516, 1344, 1262, 1107, 1049, 1013, 976, 853, 825, 745 cm^{-1}
High Resolution Mass Spectrum for $C_{10}H_9NO_2$ calcd *m/z* 175.0633, found 175.0629

(*E*)-4-(4'-nitrostyryl)-2-methylthiazole



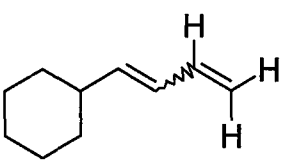
Yellow solid
R_f=0.45 (silica, hexane:ethyl acetate=50:50)
^{1}H-NMR ($CDCl_3$): δ 2.69 (s, 3H), 7.07 (s, 1H), 7.16 (d, 1H, J=15.7 Hz), 7.42 (d, 1H, J=15.8 Hz), 7.55 (d, 2H, J= 8.6 Hz), 8.13 (d, 2H, J=8.8 Hz)
^{13}C-NMR ($CDCl_3$): δ 147.20, 144.04, 130.88, 128.94, 127.35, 125.69, 124.70, 124.52, 118.10, 19.79
MS: *m/z*: 246, 223, 222, 207, 189, 181, 169, 153, 135, 127, 107, 99, 81, 79, 67, 55
FT-IR: 3424, 3065, 2922, 1589, 1506, 1333, 1108, 949, 831, 693 cm^{-1}
High Resolution Mass Spectrum for $C_{12}H_{10}N_2SO_2$ calcd *m/z* 246.0463, found 246.0452

(*E*)-ethyl-3-cyclohexyl-acrylate[45 (a)]



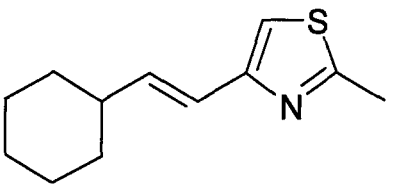
White oil
R_f=0.87 (silica, hexane:ethyl acetate=80:20)
^{1}H-NMR ($CDCl_3$): δ 1.10 (t, 3H, J=6.8 Hz), 1.20 (m, 5H), 1.68 (m, 5H), 2.08 (s, 1H), 4.10 (q, 2H, J=7.0 Hz), 5.67 (d, 1H, J=15.5 Hz), 6.86 (d, 1H, J=15.6 Hz)
^{13}C-NMR ($CDCl_3$): δ 167.55, 154.70, 119.22, 60.52, 40.77, 32.05, 26.30, 26.09, 14.66
MS: *m/z*: 183, 182, 181, 170, 160, 135, 127, 107, 85, 83, 55, 48
FT-IR: 2980, 2927, 2853, 1722, 1651, 1449, 1368, 1309, 1274, 1226, 1191, 1172, 1137, 1045, 984, 967, 852 cm^{-1}
High Resolution Mass Spectrum for $C_{11}H_{18}O_2$ calcd *m/z* 182.1306, found 182.1297

1-cyclohexyl-(*E*) or (*Z*)-1, 3-butadiene[49]



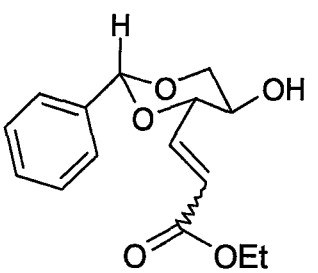
White oil
R_f=0.89 (silica, hexane:ethyl acetate=70:30)
^{1}HNMR ($CDCl_3$): δ 1.18 (m, 5H), 1.68 (m, 5H), 1.98 (m, 1H), 5.02 (dd, 1H, J=10.00, 3.2 Hz), 5.35 (dd, 1H, J=16.0, 9.6 Hz), 5.65(dd, 1H, J=16.8, 9.9 Hz), 6.00 (dd, 1H, J=16.5, 10.2 Hz), 6.28 (ddd, 1H, J=16.7, 10.1, 6.7 Hz)
^{13}CNMR ($CDCl_3$): δ 148.13, 144.46, 135.10, 121.52, 47.44, 43.65, 39.81 (d), 32.88 (d)
MS: *m/z*: 136, 135, 133, 111, 105, 92, 91, 85, 83, 81, 50, 48
FT-IR: 2925, 2853, 1731, 1592, 1452, 1384, 1165, 1038 cm^{-1}
High Resolution Mass Spectrum for $C_{10}H_{16}$, calcd *m/z* 136.1252, found 136.1252

(*E*)-4-[(2'-cyclohexyl)-vinyl]-2-methylthiazole



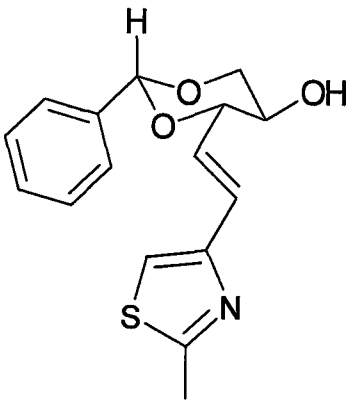
White oil
R_f=0.65 (silica, hexane:ethyl acetate=50:50)
^{1}H-NMR ($CDCl_3$): δ 1.19 (m, 5H), 1.65 (m, 5H), 2.04 (d, 1H, J= 6.8 Hz), 2.63 (s, 3H), 6.25 (d, 1H, J=15.7 Hz), 6.43 (dd, 1H, J=6.8, 15.7 Hz), 6.72 (s, 1H)
^{13}C-NMR ($CDCl_3$): δ 172.62, 161.06, 146.10, 127.36, 119.57, 59.44, 47.76, 39.56, 32.87, 26.15
MS: *m/z*: 208, 207, 178, 150, 113, 112, 55, 31
FT-IR: 3424, 3109, 2926, 2851, 1718, 1508, 1448, 1327, 1180, 968, 725 cm^{-1}
High Resolution Mass Spectrum for $C_{12}H_{17}NS$ calcd *m/z* 207.1081, found 207.1073

Ethyl (2*R*,4*S*,5*R*)-2-phenyl-4-(*E*) or (*Z*)-acrylate-*m*-dioxan-5-ol



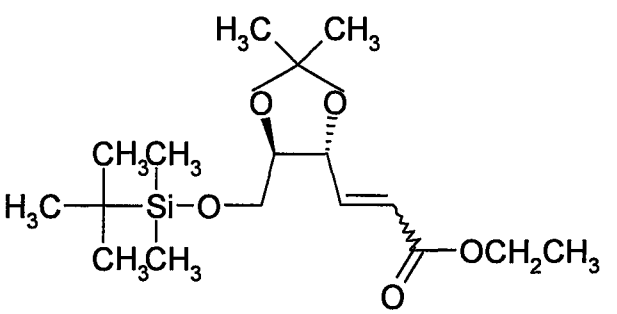
White oil
R_f=0.55 (silica, hexane:ethyl acetate=40:60)
^{1}H-NMR ($CDCl_3$): δ 1.22 (t, 3H, J=7.3 Hz), 1.55 (s, 1H), 2.12 (s, 1H), 3.62 (dd, 2H, J=7.9 Hz), 4.16(q, 2H, J=7.0 Hz), 4.26 (d, 1H, J=5.8 Hz), 5.49 (s, 1H), 6.15 (d, 1H, J=15.8 Hz), 7.08 (dd, 1H, J=15.8, 5.8 Hz), 7.29-7.45 (m, 5H)
^{13}C-NMR ($CDCl_3$): δ 173.40, 152.72, 150.21, 140.82(d), 135.75(d), 133.10(d), 129.06 (d), 107.63, 87.22, 78.69(d), 67.59, 21.00
MS: *m/z*: 280, 279, 278, 277, 267, 265, 254, 253, 247, 240
FT-IR: 3425(broad), 2972, 1686, 1654, 1542, 1458, 1373, 1304, 1086, 1052, 759, 694 cm^{-1}
High Resolution Mass Spectrum for $C_{15}H_{17}O_5$ calcd *m/z* 277.1076, found 277.1076

(2*R*,4*S*,5*R*)-2-phenyl-4-(*E*)-[2-(2'-methyl-thiazol-4'-yl)-vinyl]-*m*-dioxan-5-ol



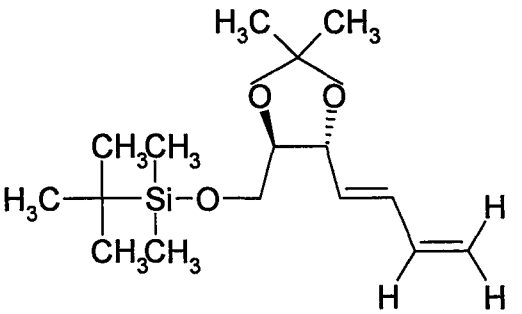
Colorless oil
R_f=0.40 (silica, hexane:ethyl acetate=40:60)
^{1}H-NMR ($CDCl_3$): δ 1.18 (s, 1H), 1.59 (s, 1H), 2.68 (s, 3H), 3.62 (dd, 2H, J=7.9 Hz), 5.78 (d, 1H, J=8.0 Hz), 6.57(s, 1H), 6.92 (d, 1H, J=16.0 Hz), 7.08 (dd, 1H, J=15.8, 8.0 Hz), 7.29-7.45 (m, 5H), 7.72(s, 1H)
^{13}C-NMR ($CDCl_3$): δ 173.18, 160.22, 158.68, 155.16, 138.27, 135.31, 130.19, 122.83, 110.22, 108.54, 86.60, 76.35, 67.12, 26.18
MS: *m/z*: 291, 255, 223, 222, 221, 207, 189, 179, 148, 105, 96
FT-IR: 3423(broad), 3056, 2922, 2853, 1685, 1655, 1508, 1458, 1372, 1261, 1217, 1181, 1068, 1024, 941, 867, 798, 758, 729, 697, 642, 602 cm^{-1}
High Resolution Mass Spectrum for $C_{16}H_{17}NSO_3$ calcd *m/z* 303.0929, found 291.9486

Ethyl 6-[(tert-butyldimethylsilyl)oxy]-4(*S*),5(*S*)-(isopropyllidenedioy)-2(*E*) or (*Z*)-hexenote[50]



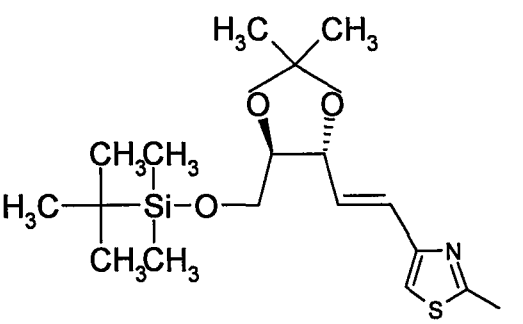
White oil
R_f=0.55 (silica, hexane:ethyl acetate=50:50)
^{1}H-NMR ($CDCl_3$): δ 0.00 (s, 6H), 0.82 (s, 9H), 1.20 (t, 3H, J=7.4 Hz), 1.35 (s, 6H), 3.67 (t, 1H, J=4.2 Hz), 3.71 (d, 2H, J=4.1Hz), 4.11 (q, 2H, J=7.3 Hz), 4.43 (d, 1H, J=12.4 Hz), 6.07 (d, 1H, J=15.7 Hz), 6.88 (d, 1H, J=15.7 Hz),
^{13}C-NMR ($CDCl_3$): δ 172.95, 151.52, 128.70, 116.69, 87.53, 69.51, 67.33, 33.65 (d), 32.65, 25.08, 21.03, 1.35
MS: *m/z*: 347, 342, 331, 330, 329, 269, 230, 229, 199, 183, 155, 117, 85, 83, 48
High Resolution Mass Spectrum for $C_{17}H_{32}SiO_5$ calcd *m/z* 344.2019, found 342.0197

7-[(Tert-butyldimethylsilyl)oxy]-5(*S*),6(*S*)-(isopropylidenedioy)-3-(*E*)-1,3-heptadiene[51]



White oil
R_f=0.60 (silica, hexane:ethyl acetate=50:50)
^{1}H-NMR ($CDCl_3$): δ 0.00 (s, 6H), 0.80 (s, 9H), 1.32 (s, 6H), 3.61 (t, 1H, J=4.2 Hz), 3.71 (d, 2H, J=4.1 Hz), 4.13 (dd, 1H, J=12.4, 2.2 Hz), 4.86 (dd, 1H, J=15.7, 8.7 Hz), 4.99 (dd, 1H, J=10.8, 8.7 Hz), 5.18 (dd, 1H, J=15.7, 8.9 Hz), 5.36 (ddd, 1H, J=16.7, 8.9, 2.2 Hz), 6.12 (dd, 1H, J=16.6, 8.7 Hz)
MS: *m/z*: 281, 278, 277, 221, 201, 183, 152, 95, 94, 77, 51
FT-IR: 2930, 2856, 1637, 1591, 1438, 1382, 1252, 1176, 1119, 1070, 857,749, 722, 694 cm^{-1}
High Resolution Mass Spectrum for $C_{16}H_{30}SiO_3$ calcd *m/z* 298.1964, found 281.0450

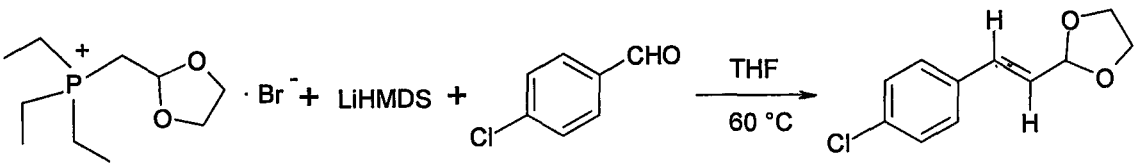
5-[(Tert-butyldimethylsilyl)oxy]-3(*S*),4(*S*)-(isopropyllidenedioy)-1-(2'-methyl-thiazol-4'-yl)-1-(*E*)-pentene



Yellow oil
R_f=0.35 (silica, hexane:ethyl acetate=50:50)
^{1}H-NMR ($CDCl_3$): δ 0.00 (s, 6H), 0.85 (s, 9H), 1.37 (s, 6H), 2.63 (s, 3H), 3.69 (d, 2H, J=3.6 Hz), 3.75 (dd, 1H, J=12.3, 2.0 Hz), 4.45 (t, 1H, J=4.2 Hz), 6.47(dd, 1H, J=15.5, 2.1 Hz), 6.58 (d, 1H, J=15.4 Hz), 6.86(s, 1H)
^{13}C-NMR ($CDCl_3$): δ 148.50, 136.29, 116.26, 114.91, 111.09, 79.56, 78.70, 63.54, 61.88, 28.30, 25.42, 18.13, 17.52, 1.84
MS: *m/z*: 371, 273, 255, 245, 187, 159, 145, 131, 97, 73
FT-IR: 3423, 2931, 2858, 1637, 1642, 1381, 1255, 1217, 1143, 1093,1007, 939, 778 cm^{-1}
High Resolution Mass Spectrum for $C_{18}H_{31}SiNSO_3$ calcd *m/z* 369.1794, found 371.1887

4.2.2. Method B

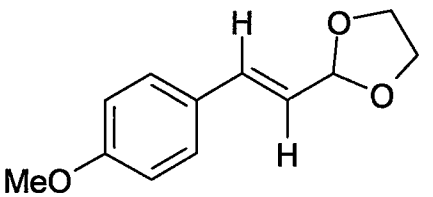
Synthesis of 2-[(*E*)-(4'-chloro)styryl]-(1,3)dioxolane



Into a dry round bottom flask was weighed 2'-(1,3-dioxolanyl)-triethylphosphonium bromide (45 mg, 0.16 mmol, 1.2 equiv.) followed by dry THF (2.0 mL THF). At room temperature a solution of LiHMDS (0.20 mL, 0.20 mmol, 1.5 equiv.) was slowly injected via syringe over 5 minutes. The reaction mixture was then stirred at 60 °C for 1 hour under argon. A solution of benzaldehyde (18 mg, 0.13 mmol, 1.0 equiv.) in 1mL THF was added in 3 minutes at 60 °C. The mixture was stirred overnight under argon. After the reaction mixture was cooled down to room temperature, an aqueous/organic (H_2O/CH_2Cl_2) workup was performed. The organic layer was washed three times and dried with Na_2SO_4. The solution was gravity filtered through cotton and Na_2SO_4 and then was washed with CH_2Cl_2 (3×4mL). The solvent was removed under reduced pressure to afford colorless solid as the crude product. The crude product was purified on a silica gel column (hexane:ethyl acetate=80:20) providing 2-[(*E*) (4'-chlorol)styryl]-(1,3)dioxolane (27.4 mg, 76%) as a white solid.

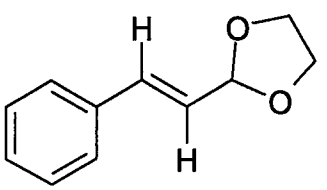
R_f=0.55 (silica, hexane:ethyl acetate=70:30)
^{1}H-NMR ($CDCl_3$): δ 3.96 (dt, 4H, J=5.1 Hz), 5.41 (d, 1H, J=5.5 Hz), 6.13 (dd, 1H, J=16.0, 5.5 Hz), 6.72 (d, 1H, J=16.0 Hz), 7.26- 7.49 (m, 4H)
^{13}C-NMR ($CDCl_3$): δ 161.84, 141.09, 140.37, 135.60, 134.95, 132.59, 110.44, 71.93
MS: *m/z*: 210, 209, 175, 140, 138, 137, 115, 103, 102, 77, 75, 73, 45
High Resolution Mass Spectrum for $C_{11}H_{11}O_2Cl$ calcd *m/z* 210.0447, found 210.0455

2-[(*E*)-(4'-methoxy)styryl]-(1,3)dioxolane



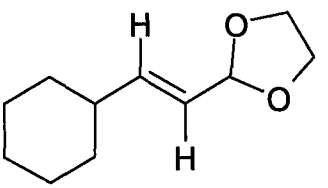
White oil
R_f=0.65 (silica, hexane:ethyl acetate=70:30)
^{1}H-NMR ($CDCl_3$): δ 3.98 (dt, 4H, J=5.7 Hz), 5.38 (d, 1H, J=6.2 Hz), 6.02 (dd, 1H, J=15.9, 6.2 Hz), 6.71(d, 1H, J=16.0 Hz), 6.84 (d, 2H, J=8.7 Hz), 7.34 (d, 2H, J=8.6 Hz)
^{13}C-NMR ($CDCl_3$): δ 166.60, 141.44, 137.19, 135.20, 133.34, 121.10, 111.05, 71.86, 62.16
MS: *m/z*: 206, 205, 175, 163, 162, 161, 147, 134, 131, 119, 108, 91, 89, 77, 63, 51
High Resolution Mass Spectrum for $C_{12}H_{14}O_3$ calcd *m/z* 206.0943, found 206.0947

2-[(*E*)-styryl]-(1, 3)dioxolane[52]



Colorless oil
R_f=0.60 (silica, hexane:ethyl acetate=70:30)
^{1}H-NMR ($CDCl_3$): δ 3.97 (dt, 4H, J=6.9 Hz), 5.43 (d, 1H, J=6.0 Hz), 6.15 (dd, 1H, J=16.1, 6.1 Hz), 6.77 (d, 1H, J=16.1 Hz), 7.28-7.58 (m, 5H)
^{13}C-NMR ($CDCl_3$): δ 159.81, 140.77, 138.15, 135.94, 135.36, 133.75, 124.18, 71.15
MS: *m/z*: 176, 175, 132, 131, 115, 104, 103, 85, 83, 77
High Resolution Mass Spectrum for $C_{11}H_{12}O_2$ calcd *m/z* 176.0837, found 176.0830

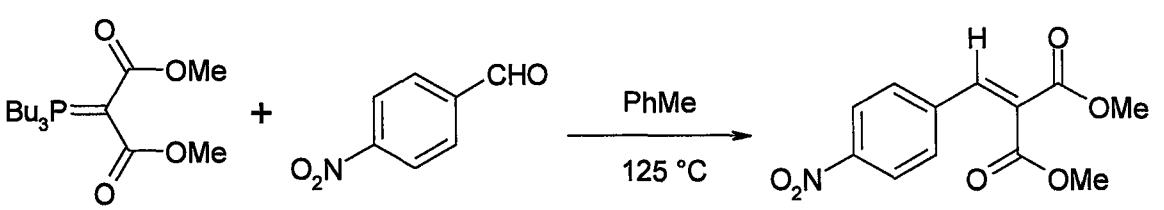
2-[(*E*)-2-cyclohexyl-vinyl]-(1,3)dioxolane



Colorless oil
R_f=0.71 (silica, hexane:ethyl acetate=70:30)
^{1}H-NMR ($CDCl_3$): δ 1.05-1.70 (m, 10H), 1.97 (d, 1H, J=6.5 Hz), 3.92 (dt, 4H, J=6.2 Hz), 5.15 (d, 1H, J=6.6 Hz), 5.46 (dd, 1H, J=15.9, 6.5 Hz), 5.88 (dd, 1H, J=15.8, 6.2 Hz)
^{13}C-NMR ($CDCl_3$): δ 150.46, 130.34, 111.39, 71.75, 46.86, 39.04, 32.80, 32.45
MS: *m/z*: 181, 139, 125, 99, 85, 83, 73, 50, 48, 46
High Resolution Mass Spectrum for $C_{11}H_{17}O_2$, calcd *m/z* 181.1228, found 181.1223

4.2.3. Method C

Synthesis of 2-(4'-nitro-styryl)-dimethyl malonate



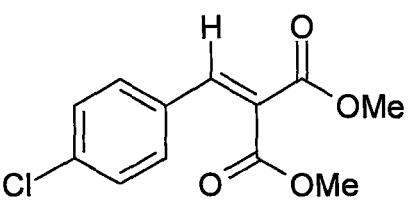
1.50 eq 1.00 eq

Into a dry round bottom flask, fitted with a condenser, was weighed dimethylmalonyltributylphosphorane (160 mg, 0.48 mmol, 1.5 equiv.) followed by dry PhMe (1.0 mL PhMe). At room temperature, a solution of 4-nitro benzaldehyde (36 mg,

0.32 mmol, 1.0 equiv.) in 1.0 mL PhMe was slowly injected via syringe over 5 minutes. The reaction mixture was then stirred at 125 °C for 48 hours under argon. The solution was cooled to room temperature. An aqueous/organic (H_2O/CH_2Cl_2) workup was performed. The organic layer was washed three times with water. The solution was gravity filtered through cotton baton and Na_2SO_4 then was washed with CH_2Cl_2 (3×4mL). The solvent was removed under reduced pressure to afford yellow slurry as the crude product. The crude product was purified on a silica gel column (hexane:ethyl acetate = 80:20) providing (43 mg, 81 %) a yellow solid.

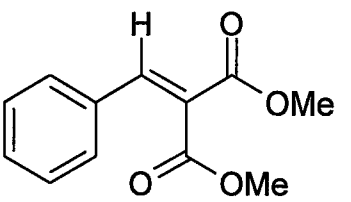
R_f=0.55 (silica, hexane:ethyl acetate=80:20)
^{1}H-NMR ($CDCl_3$): δ 3.83 (s, 3H), 3.87 (s, 3H), 7.57 (d, 2H, J=8.4 Hz), 7.79 (s, 1H), 8.24 (d, 2H, J=8.5 Hz)
^{13}C-NMR ($CDCl_3$): δ 172.87, 170.52, 155.29, 146.31, 136.72, 135.78, 130.84, 59.89
MS: *m/z*: 265, 250, 234, 206, 205, 203, 175, 174, 166, 147, 131, 115, 101, 75, 59
High Resolution Mass Spectrum for $C_{12}H_{11}NO_6$, calcd *m/z* 265.0586, found 265.0591

2-(4'-chlorobenzylidene)-dimethyl malonate



White solid
R_f=0.62 (silica, hexane:ethyl acetate=80:20)
^{1}H-NMR ($CDCl_3$): δ3.84 (s, 3H), 3.88 (s, 3H), 7.35 (m, 4H) 7.71 (s, 1H)
^{13}C-NMR ($CDCl_3$): δ173.69, 171.10, 148.32, 143.64, 138.05, 137.75, 132.82, 59.63
MS: *m/z*: 254, 223, 196, 194, 163, 155, 136, 121, 101, 91, 77, 59, 43
High Resolution Mass Spectrum for $C_{12}H_{11}O_4Cl$, calcd *m/z* 254.0346, found 254.0339

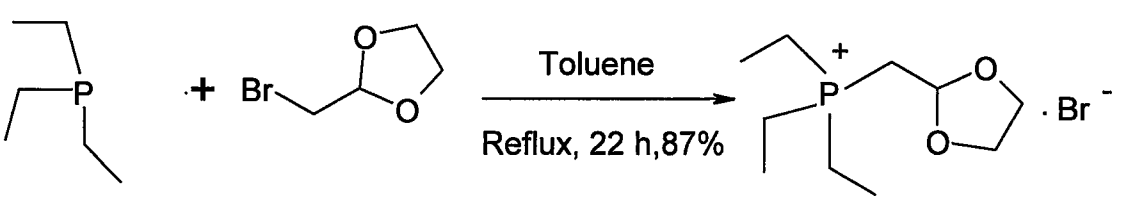
2-styryl-dimethyl malonate



White oil
R_f=0.70 (silica, hexane:ethyl acetate=80:20)
^{1}H-NMR ($CDCl_3$): δ 3.84 (s, 3H), 3.89 (s, 3H), 7.35-7.49 (m, 1H), 7.54 (d, 2H, J=8.9 Hz), 7.77 (s, 1H), 8.16 (d, 2H, J=8.7 Hz)
^{13}C-NMR ($CDCl_3$): δ 173.99, 171.33, 149.81, 140.52, 137.27, 135.72, 132.27, 59.55
MS: *m/z*: 221, 220, 189, 188, 171, 161, 160, 130, 129, 122, 121, 105, 85, 83, 77, 48
High Resolution Mass Spectrum for $C_{12}H_{12}O_4$ calcd *m/z* 220.0735, found 220.0738

4.2.4. Procedure for synthesis of phosphonium salts

Synthesis of 2'-(1, 3-dioxolanyl)-triethylphosphonium bromide



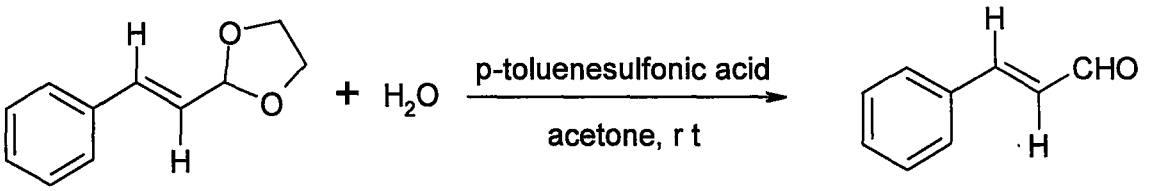
Into a dry 50mL round bottom flask, fitted with a condenser, was weighed 2-bromomethyl-1, 3-dioxolane (3.3402 g, 20 mmol, 1.0 equiv.) followed by dry toluene (5.0 mL toluene). At room temperature triethylphosphine (20 mmol, 1.0 equiv.) was slowly injected via syringe over 5 minutes. The reaction mixture was then stirred at

120°C for 22 hours under argon. The solution was cooled to room temperature. Toluene was removed under reduced pressure to afford a yellow slurry as the crude product. Diethyl ether (20 mL) was added and the slurry chilled in the refrigerator for 1 hour. The white crystalline solid was filtered by suction and dried under high vacuum for two hours, yielding the hygroscopic phosphonium salt, 4.9508 g, 86.8%.

^{1}H-NMR ($CDCl_3$): δ 1.23 (dt, 9H, J=7.6, 4.2 Hz), 2.54 (dq, 6H, J=7.6, 4.2 Hz), 3.03 (dd, 2H, J=9.6, 4.2 Hz), 3.85-4.1 (m, 4H), 5.21 (m, 1H, J=9.5, 4.3 Hz)
^{13}C-NMR ($CDCl_3$): δ 105.75, 71.98, 30.5 (d), 20.4 (d), 13.01
^{31}P-NMR ($CDCl_3$): δ 41.00
MS: *m/z*: 205, 161, 118, 88, 79
High Resolution Mass Spectrum for $C_{10}H_{22}O_2BrP$ calcd *m/z* 284.0540, found 205.1357

4.3. Procedure for hydrolysis of acetal.

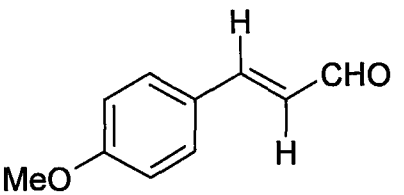
Synthesis of cinnamaldehyde[53]



Into a round bottom flask was weighed 2-[(*E*)-styryl]-(1, 3)dioxolane (50 mg, 0.28 mmol, 1.0 equiv.), p-toluenesulfonic acid (8 mg, 0.04 mmol, 0.15 equiv.). 2 mL acetone and 2 mL H_2O were added at 0 °C. The reaction mixture was then stirred at 0 °C for 20 minutes and then at 22 °C for 10 minutes. An aqueous/organic (H_2O/CH_2Cl_2) workup was performed. The organic layer was washed three times and dried with Na_2SO_4. The solution was gravity filtered through cotton and Na_2SO_4 and then was washed with CH_2Cl_2 (3×2mL). The solvent was removed under reduced pressure to afford white oil as the crude product. The crude product was purified on a silica gel column (hexane:ethyl acetate=80:20) providing cinnamaldehyde (30 mg, 80%) as white oil.

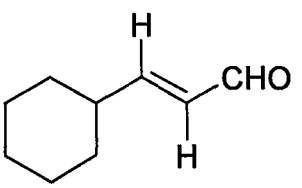
R_f=0.60 (silica, hexane:ethyl acetate=80:20)
^{1}H-NMR ($CDCl_3$): δ 6.72 (dd, 1H, J=16.3, 7.8 Hz), 7.45-7.50 (m, 5H), 7.56 (d, 1H, J=15.9 Hz), 9.71 (d, 1H, J=7.8 Hz)
^{13}C-NMR ($CDCl_3$): δ 200.58, 159.66, 140.81, 138.11, 135.93, 135.33
MS: *m/z*: 132, 103, 87, 85, 83, 77, 48, 46
High Resolution Mass Spectrum for C_9H_8O calcd *m/z* 132.0575, found 132.0572

4-methoxycinnamaldehyde[54]



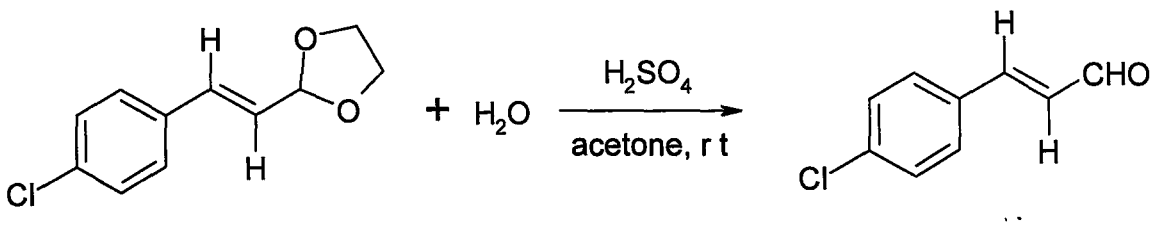
Yellow solid
R_f=0.50 (silica, hexane:ethyl acetate=80:20)
^{1}H-NMR ($CDCl_3$): δ 3.75 (S, 3H), 6.59 (dd, 1H, J=15.9, 7.8 Hz), 6.92 (d, 2H, J=8.7 Hz), 7.40 (d, 1H, J=15.9 Hz), 7.50 (d, 2H, J=8.7 Hz), 9.62 (d, 1H, J=7.7 Hz)
^{13}C-NMR ($CDCl_3$): δ 200.58, 169.02, 159.60, 138.81, 137.19, 135.45(d), 121.38, 62.28
MS: *m/z*: 163, 162, 161, 147, 136, 131, 119, 108, 91, 78, 77
High Resolution Mass Spectrum for $C_{10}H_{10}O_2$ calcd *m/z* 162.0680, found 162.0677

3-cyclohexyl-2-(*E*)-allyl aldehyde[55]



Yellow solid
R_f=0.65 (silica, hexane:ethyl acetate=80:20)
^{1}H-NMR ($CDCl_3$): δ 1.59 (m, 10H), 2.33 (d, 1H, J=3.7 Hz), 6.77 (dd, 1H, J=15.7, 7.6 Hz), 7.15 (dd, 1H, J=15.6, 3.5 Hz), 9.49 (d, 1H, J=7.8 Hz)
^{13}C-NMR ($CDCl_3$): δ 158.02, 151.40, 134.40(d), 79.66, 50.20, 40.80(d), 33.51
MS: *m/z*: 147, 135, 111, 96, 95, 81, 67, 48
High Resolution Mass Spectrum for $C_9H_{14}O$ calcd *m/z* 138.1044, found 135.1131

Synthesis of 4-chlorocinnamaldehyde[53]

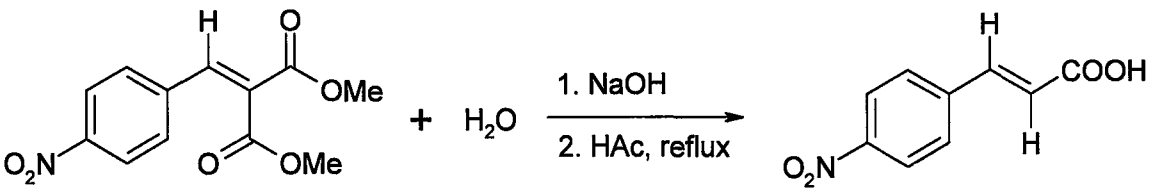


Into a round bottom flask was weighed 2-[(*E*) (4'-chloro)styryl]-(1,3)dioxolane (31.5 mg, 0.15 mmol, 1.0 equiv.), 98% sulfuric acid (14.8 mg, 8 μL, 0.15 mmol, 1.0 equiv.). 2 mL acetone and 1 mL H_2O were added at 0 °C. The reaction mixture was then stirred at 0 °C for 20 minutes then at 22 °C for 36 hours. An aqueous/organic (H_2O/CH_2Cl_2) workup was performed. The organic layer was washed three times with water. The solution was gravity filtered through cotton and Na_2SO_4 and then was washed with CH_2Cl_2 (3×2mL). The solvent was removed under reduced pressure to afford white oil as the crude product. The crude product was purified on a silica gel column (hexane:ethyl acetate=80:20) providing 4-chlorocinnamaldehyde (21.6 mg, 86%) as a yellow solid.

R_f=0.40 (silica, hexane:ethyl acetate=80:20)
^{1}H-NMR ($CDCl_3$): δ 6.22 (d, 1H, J=15.8 Hz), 6.84 (dd, 1H, J=15.5, 7.5 Hz), 7.32 (m, 4H), 9.71 (d, 1H, J=7.4 Hz)
^{13}C-NMR ($CDCl_3$): δ 169.81, 146.54, 141.51(d), 137.66, 135.91, 135.18, 133.99
MS: *m/z*: 168, 167, 166, 146, 145, 137, 131, 103
High Resolution Mass Spectrum for C_9H_7OCl calcd *m/z* 166.0185, found 166.0189

4.4. Procedure for hydrolysis and decarboxlation of of malonate

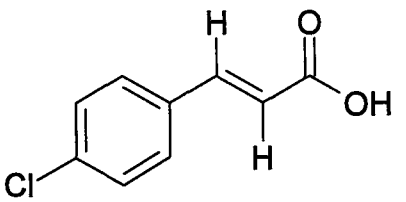
Synthesis of 4-nitrocinnamic acid



Into a round bottom flask were weighed 2-(4'-nitro-styryl)-dimethyl malonate (20.1 mg, 0.075 mmol, 1.0 equiv.), NaOH (6.1 mg, 0.15 mmol, 2.0 equiv.). 2 mL H_2O was added at 22 °C. The reaction mixture was then stirred at 22 °C overnight. Acetic acid (15 mg, 15 μL, 0.225 mmol, 3.0 equiv.) was added to the reaction mixture and then stirred at 110 °C for 24 hours. An aqueous/organic (H_2O/CH_2Cl_2) workup was performed. The organic layer was washed three times with water. The solution was gravity filtered through cotton and Na_2SO_4 then was washed with CH_2Cl_2 (3×2mL). The solvent was removed under reduced pressure to afford white oil as the crude product. The crude product was purified on a silica gel column (hexane:ethyl acetate=20:80), providing 4-nitrocinnamic acid (8.8 mg, 60%) as an orange solid.

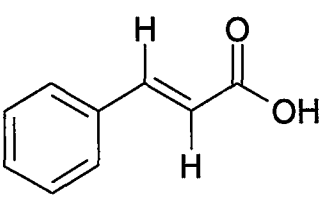
R_f=0.20 (silica, hexane:ethyl acetate=20:80)
^{1}H-NMR ($CDCl_3$): δ 6.97 (d, 1H, J=15.6 Hz), 7.92 (d, 1H, J=15.7 Hz), 8.00 (m, 4H), 10.08 (s, 1H)
^{13}C-NMR ($CDCl_3$): δ 196.51, 142.54, 137.55, 132.42, 129.89, 122.80, 118.59
MS: *m/z*: 193, 192, 191, 176, 174, 166, 130, 102, 92, 62
High Resolution Mass Spectrum for $C_9H_7O_4N$ calcd *m/z* 193.0375, found 193.0692

4-chlorocinnamic acid



R_f=0.27 (silica, hexane:ethyl acetate=20:80)
^{1}H-NMR ($CDCl_3$): δ 6.44 (dd, 1H, J=16.0, 7.8 Hz), 7.28-7.53 (m, 4H), 7.72 (dd, 1H, J=16.1, 7.8 Hz)
^{13}C-NMR ($CDCl_3$): δ 178.35, 152.29, 142.21(d), 137.22(d), 134.91, 133.33, 125.46
MS: *m/z*: 184, 182, 181, 165, 149, 137, 102, 101, 75, 73
High Resolution Mass Spectrum for $C_9H_7O_2Cl$ calcd *m/z* 182.0135, found 182.0128

cinnamic acid

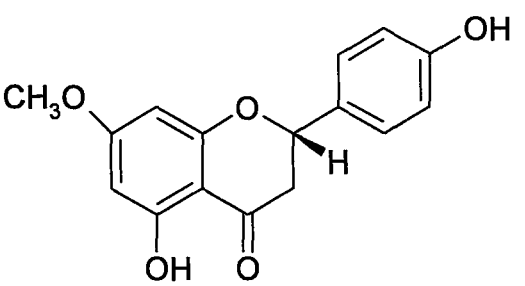


R_f=0.36 (silica, hexane:ethyl acetate=20:80)
^{1}H-NMR ($CDCl_3$): δ 6.52 (d, 1H, J=14.6 Hz), 7.42-7.66(m, 4H), 8.11 (d, 1H J=14.7 Hz)
^{13}C-NMR ($CDCl_3$): δ 178.65, 149.82, 140.62, 137.03, 136.08, 135.72, 135.32
MS: *m/z*: 143, 135, 129, 122, 115, 106, 105
High Resolution Mass Spectrum for $C_9H_8O_2$ calcd *m/z* 148.052439, found 143.0853

4.5. Procedure for purification of natural products.

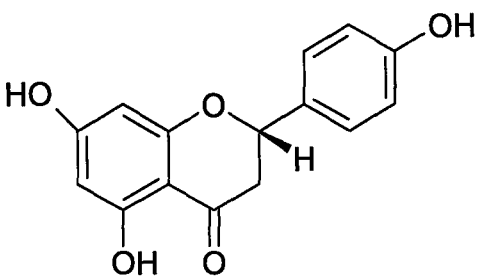
The fraction (0.2095 g) from *Prunus sp* was subjected to a silica gel column ø20mm×350mm (Hexanes/Ethyl acetate=70/30), followed by a silica gel column (DCM), to separate Sakuranetin (0.0524 g, 25%, yellow solid), Naringenin (0.0177 g, 8.4%, white solid) and (2*S*)-7-methoxy-6-hydroxyflavanone (0.0290 g, 14.5%, white solid).

Sakuranetin (2*S*)-5, 4'-dihydroxy-7-methoxyflavanone



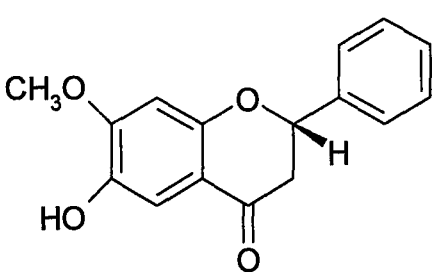
Melting point: 90-92°C
R_f=0.46 (silica, hexane:ethyl acetate=70:30)
^{1}H-NMR ($CDCl_3$): δ 2.78 (dd, 1H, J=17.4, 3.0 Hz), 3.09 (dd, 1H, J=16.8, 13.2 Hz), 3.80 (s, 3H), 5.35 (dd, 1H, J=13.2, 3.0 Hz), 6.05 (dd, 2H,J=15.1, 2.4 Hz), 6.88 (d, 2H, J=8.4 Hz), 7.32 (d, 2H, J=8.4 Hz), 12.02 (s, 1H)
^{13}C-NMR ($CDCl_3$): δ 196.28, 168.17, 164.25, 163.06, 156.46, 130.50, 128.09, 115.82, 110.27, 95.25, 94.41, 79.13, 55.83, 43.30
MS: *m/z*: 286, 285, 207, 193, 180, 167, 166, 138, 129, 120, 95, 73, 57
High Resolution Mass Spectrum for $C_{16}H_{14}O_5$ calcd *m/z* 286.0841; found 286.0801
FT-IR: 3421(broad), 2924, 1643, 1618, 1576, 1518, 1449, 1356, 1194, 1157, 1091, 886, 833 cm^{-1}

Naringenin (2*S*) - 5, 7, 4'-trihydroxyflavanone



Melting point: 243-245°C
R_f=0.33 (silica, hexane:ethyl acetate=70:30)
^{1}H-NMR ($CDOD_3$): δ 2.67 (dd, 1H, J=14.1, 3.0 Hz), 3.10 (dd, 1H, J=14.2, 7.1 Hz), 5.32 (dd, 1H, J=9.9, 2.9 Hz), 5.88 (d, 2H, J=1.0 Hz), 6.80 (d, 2H, J=8.6 Hz), 7.30 (d, 2H, J=8.6 Hz), 8.02 (s, 1H)
^{13}C-NMR ($CDOD_3$): δ 203.22, 173.77, 170.88, 170.30, 164.44, 136.80, 136.48, 134.46, 121.71, 102.43, 101.55, 85.89, 49.44
MS: *m/z*: 272, 171, 271, 179, 153, 152, 124, 120, 119, 91, 57

(2*S*)- 7-methoxy-6-hydroxyflavanone



Melting point: 187-188°C
R_f=0.20 (silica, hexane:ethyl acetate=70:30)
^{1}H-NMR ($CDCl_3$): δ 2.85 (dd, 1H, J=14.1, 3.3 Hz), 3.10 (dd, 1H, J=12.8, 4.5 Hz), 3.87 (s, 3H), 5.48 (dd, 1H, J=12.6, 3.3 Hz), 6.15 (s, 1H), 6.51 (s, 1H), 7.43 (m, 5H), 11.88 (s, 1H)
^{13}C-NMR($CDOD_3$): δ 195.12, 176.30, 166.40, 165.18, 168.65, 153.57, 136.84, 135.74, 132.78, 130.00, 129.85, 126.22, 86.45, 50.81, 36.66
MS: *m/z*: 241, 240, 226, 225, 207, 195, 165, 149, 119, 93, 85, 65

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