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THE SYNTHESIS OF Q,B-UNSATURATED ESTERS FROM KETONES WITH ETHYL BIS (TRIFLUOROETHYL) -- PHOSPHONOACETATE presented by

EZZEDDINE BOUHLEL

has been accepted towards fulfillment of the requirements for

Master\_degree in \_\_organic chemistry

Michael Pathke Major professor

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#### THE SYNTHESIS OF $\alpha$ , $\beta$ -UNSATURATED ESTERS FROM KETONES WITH ETHYL BIS(TRIFLUOROETHYL)PHOSPHONOACETATE

ΒY

EZZEDDINE BOUHLEL

#### A THESIS

#### Submitted to Michigan State University in partial fulfillment of the requirements for the degree of

#### MASTER OF SCIENCE

Department of Chemistry

#### ABSTRACT

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#### THE SYNTHESIS OF $\alpha$ , $\beta$ -UNSATURATED ESTERS FROM KETONES WITH ETHYL BIS(TRIFLUOROETHYL)PHOSPHONOACETATE

BY

#### **BZZEDDINE BOUHLEL**

In the presence of triethylamine and lithium bromide, ethyl bis(trifluoroethyl)phosphonoacetate reacts with a variety of ketones including acetophenone and with benzaldehyde to give  $\alpha$ ,  $\beta$ -unsaturated esters in good yields.

Under the same conditions ethyl bis(trifluoroethyl)phosphonoacetate was found to be unreactive towards hindered ketones.

Compared to procedures with triethylphosphonoacetate ethyl bis(trifluoroethyl)phosphonoacetate gives better results with ketones including acetophenone which are normally unreactive towards the Horner-Wadsworth-Emmons olefinations.

**ii** 

#### TO MY DAUGHTER, ZEINEB AND MY PARENTS

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#### ACKNOWLEGDEMENTS

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#### INTRODUCTION

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#### INTRODUCTION

The reaction of carbonyl compounds with phosphorus ylides has had wide application in the synthesis of olefins. One of the first used forms of this group of reactions is the Wittig reaction in which carbonyl compounds are treated with phosphonium ylides 1 to form an olefin and phosphine oxide (Eq 1).<sup>1,2</sup>



The scope, mechanism and stereochemistry of this reaction have been investigated in detail and these studies have been the subject of many publications.<sup>3-20</sup>

There are, however, several limitations to the Wittig olefin synthesis, and this has led to the development of various modified forms of this reaction. These involve the use of other organophosphorus compounds which lend themselves to carbanion formation.

One of these modifications of the Wittig synthesis was developed by Horner, et.  $al.^{21}$ , and by Wadsworth and Emmons<sup>22</sup> (Eq. 2).

$$(RO)_{2}P(O)CH_{2}E \xrightarrow{BASE} R^{2}R^{3}CO R^{2}R^{3}C=CHE$$

$$+ (2)$$

$$(RO)_{2}PO_{2}$$

R = alkyl or phenyl
B = Resonance-stabilizing group.

The modified Wittig reaction, the Horner-Wadsworth-Emmons olefination reaction (the HWE reaction), possesses the following advantages over the conventional Wittig reaction:

a) Phosphonate carbanions are known to be more nucleophilic than similarly substituted phosphonium ylides.<sup>22,23</sup> The greater reactivity of phosphonate anions as compared to phosphorus ylides is due to the fact that the phosphonate group is not as effective in stabilizing a negative charge because of "back donation" from oxygen.

- b) The water-soluble phosphate ion formed in the HWE reaction is much easier to separate from the olefin product.
- c) The enhanced reactivity of the phosphonate carbanions allows much the *c*-carbon to be elaborated by alkylation (Eq. 3), whereas the phosphonium ylides do not generally undergo easy alkylation.

 $(RO)_2 P(O)CHE + R^1 X \longrightarrow (RO)_2 P(O)CHR^1 E + X^-$  (3)

d) Phosphonates are readily available<sup>24</sup> from the Arbuzov reaction or the Michaelis-Becher reaction. The former, involving the reaction of trialkylphosphite with an alkylhalide, is the most commonly used method. Thus, the phosphonates are less expensive than the corresponding alkylphosphonium salts.

The HWE reaction can be used to synthesize a variety of compounds. It has been used in the intermolecular synthesis of ring compounds containing butenolide moieties<sup>25</sup> (Eq. 4). With epoxides it yields substituted cyclopropanes<sup>26</sup> (Eq. 5).

The HWE reaction has been used in many industrial processes and bis-phosphonates have been tested as polymerizing reagents.<sup>27</sup>





One of the most used and important HWE reagents, triethylphosphonoacetate 2 employs an ester function as the electron-withdrawing group.

(EtO)2P(0)CH2CO2Et

#### 2

Triethylphosphonoacetate 2 and closely related derivatives have been applied to the synthesis of many natural products including prostaglandins<sup>28</sup>, juvenile hormones<sup>29</sup> and many isoprenoid compounds<sup>30</sup> including carotene.<sup>31</sup>

The mechanism widely accepted for the HWE reaction is analogous to that of the Wittig reaction (Eqs. 6-9).

The first step, the formation of the anion 3 stabilized by an electron-withdrawing group (ester function in the case of 2) and the P(0) function, may or may not be an



equilibrium process depending upon the base used. With sodium hydride or other strong bases, anion formation is irreversible.

The second step is a reversible aldol condensation that gives two possible diasteriomeric oxyanions (4 and 5). There is no direct evidence that cyclic intermediates are involved but it is thought that the oxyanions decompose via a syn elimination in an irreversible fashion to give olefin (Eqs. 8 and 9). The erythro form 4 gives the Z olefin, while the threo form 5 leads to the E olefin.<sup>32</sup>

In contrast to aldol condensations<sup>33</sup> the HWE olefination reaction using triethylphosphonoacetate 2 gives the olefinic product regiospecifically and in one step. The formation of  $\beta$ ,  $\gamma$ -unsaturated esters complicates the acid-catalyzed dehydration of  $\beta$ -hydroxyesters formed by aldol reactions (Eq. 10).<sup>34</sup>



In the case of the HWE olefination reaction, only a few cases of the formation of  $\beta$ ,  $\gamma$ -unsaturated esters have been reported.<sup>35</sup>

The HWE olefination reaction using 2 often gives the olefinic product with a high degree of stereochemical control of the newly-made double bond. In many cases, only B esters are formed when triethylphosphonoacetate 2 reacts with aliphatic aldehydes (Eqs. 11 and 12).<sup>36</sup>



The E:Z ratio of the product olefin is dependent on temperature (Eqs. 13-15).<sup>37a</sup>



In general, thermodynamically-controlled HWE olefination reactions give E olefins. This is a result of thermodynamic control upon the reversible formation and interconversion of the erythro and three oxyanions 4 and 5 (Eqs. 8 and 9) and their decomposition to olefins. Kinetically-controlled HWE olefination reactions usually give the Z olefins<sup>37</sup>, presumably because oxyanion 4 is formed faster than oxyanion 5.

Steric requirements are very important in the HWE olefination reaction. The phosphonate anions are more reactive towards aldehydes than ketones. Some ketones are totally unreactive towards the phosphonate anions. Simple cyclohexanones are normally reactive towards the HWE olefination reaction but cyclohexanones, substituted at the 2 position, are unreactive if the substituent is in the equatorial position.<sup>38,39</sup> In steroidal systems, the phosphonate anion 3 reacts with 3-keto steroids but give no reaction with 6-keto, 7-keto, 17-keto or 20-keto steroids.<sup>38</sup>

(EtO)<sub>2</sub>P(O)-CH-CO<sub>2</sub>Et

3

The generation of the phosphonate anion 3 usually involves the use of strong bases such as sodium hydride, lithium diisopropylamide (LDA) or metal alkoxides.

These procedures are expensive and the bases used may react with sensitive functional groups in the substrate and/or the reagent.

Recently, the HWB olefination reaction was carried out under mild conditions using triethylamine as base in the presence of metal salts (Eq. 16).<sup>40</sup>



It is assumed that metal cation coordination enhances the acidity of 2 allowing anion formation with weak bases. In the presence of a potassium cation, the pk of triethylphosphonoacetate 2 has been found to be 19.2 (dimethylsulfoxide solution) and, in the presence of a lithium cation, 12.2 (diglyme solution).<sup>41</sup> The difference in acidity can be attributed to tighter chelation of the lithium cation resulting in a stronger metal-oxygen bond in the enolate 6. Thus, the nature of the metal M has a great influence on the stability of 6 and on the acidity of 2.

Phosphonates, which have no carboethoxy group, are expected to be poorer chelating agents with metal cations. The acidities of these show a less-pronounced dependency on the nature of the metal cation present. For example, phosphonate 7, which has no carboethoxy group, has only a 4

pk unit difference in the presence of lithium and potassium cations.

#### (EtO)<sub>2</sub>P(O)CH<sub>3</sub>

#### 7

For the modified HWE olefination reaction<sup>40</sup> using triethylamine and metal salts, it was found that the use of lithium and magnesium halides promotes the reaction and that the reagent obtained with lithium halides is more reactive than the reagent obtained with magnesium halides.

Excellent yields were obtained with aldehydes and with the reactive ketone cyclohexanone. Unfortunately, simple methylketones such as acetophenone or acetone were unreactive to triethylphosphonoacetate 2 in the presence of either magnesium bromide or lithium bromide. We considered that the lack of reactivity observed with ketones is due to a very slow rate of decomposition of the betaine intermediate.

Increasing the rate of decomposition of the betaine seems to be the solution to this problem. We considered that this can be accomplished by changing the structure of the phosphonate by adding electron-withdrawing groups or using five atom rings on phosphorus.

Electron-withdrawing groups X (Eq. 17.) would activate the P(0) group towards alkoxide attack by withdrawing

electron density from phosphorus and, thus, speeding up the formation and decomposition of the cyclic intermediate 8.



The use of phosphonates bearing five atom rings<sup>42</sup> on phosphorus should: (a) lead to more rapid closure to a fivecoordinate intermediate 9 (Eq. 18) (release of ring strain upon passing from the tetrahedral to the trigonalbipyramid structure); and (b) reduce the rate of inversion to the phosphonate and carbonyl compound for the same reasons.



Structures 10-13 are phosphonates that have either electron-withdrawing groups or five atom rings on phosphorus which we considered could be used as olefinating reagents in the HWE olefination reaction.



There are two compelling reasons for using 11 as the olefinating reagent in the HWE reaction :

- 1. The synthesis of 11 is described in the literature.<sup>43</sup>
- 2. W. Clark Still used 11 to carry out the stereoselective synthesis of Z  $\alpha$ -unsaturated esters from a variety of aliphatic and aromatic aldehydes. It was concluded that the two powerful electron-withdrawing groups (CF<sub>3</sub>CH<sub>2</sub> groups) are responsible for the Z selectivity by speeding up the elimination of the initial adduct.

With these facts in hand, we decided to synthesize 11 (Eqs. 19 and 20) and examine its properties as an olefinating reagent with ketones in the presence of triethylamine and metal salts (Eq. 21). It was hoped that

good yields of the corresponding olefins could be obtained under these conditions.

$$(EtO)_2 P(O)CH_2 CO_2 Et + 2PCI_5 \longrightarrow CI_2 P(O)CH_2 CO_2 Et$$
 (19)  
14

14 + 
$$2CF_3CH_2OH$$
 \_\_\_\_\_ ( $CF_3CH_2O)_2P(O)CH_2CO_2Et$  (20)  
11

$$R^{1}CR^{2} + MX + 11 \xrightarrow{Et_{3}N} R_{1}R_{2}C = CHCO_{2}Et$$
 (21)

**RESULTS AND DISCUSSION** 

#### **RESULTS AND DISCUSSION**

The reaction of 3-pentanone with the standard phosphonate 2 in the presence of triethylamine and lithium bromide in tetrahydrofuran (Eq. 22) was examined.



The GC yield of the corresponding  $\alpha$ ,  $\beta$ -unsaturated ester (ethyl-3-ethyl-2-pentenoate) was (5%) which confirm the unreactivity of simple methylketones with triethylphosphonoacetate 2. The same reaction was conducted with 11 (Eq. 23) and the GC yield was (70%).



The results of these two reactions demonstrate the potential of 11 as an olefinating reagent in the HWE reaction.

Using the conditions from our study on 3-pentanone with 11, we studied the reaction of benzaldehyde and a variety of ketones with 11 and the results are shown in Table 1.

Lithium bromide i s partially soluble in tetrahydrofuran. However, addition of ethyl bis(trifluoroethyl)phosphonoacetate **11** resulted in complete dissolution of the salt and homogeneous solution. Addition of triethylamine to this mixture resulted in instantaneous formation of a precipitate presumed to be ET<sub>3</sub>N.HBr. Subsequent addition of the carbonyl substrate to the mixture resulted in no change of the precipitate formed.

Good yields are obtained with benzaldehyde and with simple ketones (Entries 1-6). However, ketones such as 2,4dimethyl-3-pentanone, 2,4-tetramethyl-3-pentanone or 3,3dimethyl-2-butanone (Entries 7-9) fail to react. In the case of benzaldehyde (Entry 5), a 56:44 Z/E ratio of the product *a*, *B*-unsaturated ester (ethyl cin**namate**) was obtained. Acetophenone (Entry 6) gave 53:47 Z/E ratio of the  $\alpha$ ,  $\beta$ -unsaturated ester (2-butanoic acid and 3-phenylester). High B/Z ratios of  $\alpha$ ,  $\beta$ -unsaturated esters have been reported HWE olefination reaction for the using triethylphosphonoacetate 2, triethylamine and different metal salts including lithium bromide.<sup>40</sup> For example benzaldehyde gave only (E) ethyl cinnamate. This procedure

<u>Table 1</u>. Reaction of a Variety of Carbonyl Compounds with 11 in the Presence of Triethylamine and Lithium Bromide.

$$R^{1}CR^{2} + L1Br + 11 \xrightarrow{Et_{3}N} R^{1}R^{2}C=CHCO_{2}Et$$

$$24 hr$$

Entry	Carbonyl Compound	Producta	Yield <sup>b</sup> %	E/Z <sup>c</sup> ratio	
1	Cyclohexanone	C02Et	79 (68)		
2	Cyclopentanone	CO2Et	71 (52)		
3	3-Pentanone	Et CO <sub>2</sub> Et	73 (60)		
4	Benzophenone	Ph Ph CO <sub>2</sub> Et	51		
5	Benzaldehyde		82 (65)	44/56	
6	Acetophenone	Ph Me CO <sub>2</sub> Et	75	47/53	
7	Pinacolone		0		
8	2,4-dimethy1-3-pentanone		0		
9	2,4-tetramethy1-3-pentanone		0		

<sup>a</sup> All reactions carried out at 25°C on a 5 mmol scale for 24 hr reaction period.

<sup>b</sup> Yields of products determined by GC analysis. Yields in parentheses are isolated yields.

<sup>c</sup> Determined by GC and <sup>1</sup>H-NMR analysis.

using 11 appears to favor the Z isomer over the E. The formation of the Z isomer in a greater proportion over the E is probably due to the faster elimination of the initial adduct when compared with adduct equilibrium (equilibration of 4 to 5, Eq. 8 and 9).

In order to compare our procedure using 11 with the original procedure using 2, we compare Entries 2 and 6 in Table 1 to Entries 3 and 5 in Table 2. It is clear that the reactivity towards ketones was enhanced considerably when using phosphonate 11 as the olefinating reagent.

further of As test procedure. a our new ethyl bis(trifluoroethyl)phosphonoacetate ll was reacted with cyclohexanone in the presence of lithium diisopropylamine (LDA) a classical strong base. The results of this reaction are shown in Table 3.

The results shown in Table 1 (weak base triethylamine) in the presence of a metal salt (lithium bromide) seem much better than those with LDA shown in Table 3.

The purpose of this study was to increase the yields of  $\alpha$ ,  $\beta$ -unsaturated esters from ketones using a weak base procedure and it appears that this goal has been achieved. This procedure using 11, triethylamine and lithium bromide has several advantages over other related HWE procedures.

Table 2.	Reaction of a Variety of Carbonyl	Compounds with	ith 2	in the	Presence	of
	Triethylamine and Metal Halides.*					

 $\begin{array}{c} 0 \\ \parallel \\ \mathbb{R}^{1}\mathbb{C}\mathbb{R}^{2} + \mathbb{M}\mathbb{X} + 2 \end{array} \xrightarrow{\text{Bt}_{3}\mathbb{N}} \mathbb{R}^{1}\mathbb{R}^{2}\mathbb{C} = \mathbb{C}\mathbb{H}\mathbb{C}\mathbb{O}_{2}\mathbb{E}\mathbb{t} \\ \text{ solvent, } 25^{\circ}\mathbb{C} \\ 3 \text{ hours} \end{array}$ 

Bntry	Carbonyl Compound	<b>Metal</b> Halide	Solvent	Product	Yield, % <sup>b</sup>
1	Се Н5 СНО	LiBr	(CH3CN)	C <sub>6</sub> H <sub>5</sub> CH===CHCO <sub>2</sub> Bt	84
		MgBr <sub>2</sub>	(THF)		85
2	Cyclohexanone	LiBr	(CH3CN)	(CH <sub>2</sub> )5C=CHCO <sub>2</sub> Et	85
3	Cyclopentanone	LiBr	(CH3CN)	(CH <sub>2</sub> ) <sub>4</sub> C=CHCO <sub>2</sub> Bt	15
4	Acetone	LiBr MgBr2	(CH₃CN) (THF)		0 0
5	Acetophenone	LiBr MgBr2	(CH3CN) (THF)		0 0

Reaction at 25°C for 12h, 25 mmol scale (carbonyl compound:7:Et<sub>3</sub>N:metal halide - 1:1:1.1:1.2)

<sup>b</sup> Isolated yield, based on weight of distilled product.





×->



Entry	THF (mL)	T1 (°C)	tı (mn)	T2 (°C)	t2 (hr)	yield (%)
1	25	0	15	25	1	30
2	5	0	15	25	1	30
3	5	-78	5	25	1	65
4	5	-78	15	25	2	51
5	25	-78	5	25	5	55
6	5	-78	5	-78	0	16
						· · · · · · · · · · · · · · · · · · ·

-Inexpensive and readily-handled base.

- -Mild conditions (weak base, room temperature) used to carry out the reactions.
- -Good yields obtained with simple ketones (usually unreactive towards the HWE olefination reactions) and thus a new route is opened to the synthesis of  $\alpha$ ,  $\beta$ unsaturated esters from ketones.
- -The enhancement of the Z/E ratio of  $\alpha$ ,  $\beta$ -unsaturated esters isomers and, thus, a procedure that can be used for the preparation of Z isomers which are usually difficult to obtain.

The major disadvantage of our procedure is the somewhat difficult preparation of the olefinating reagent ethyl bis(trifluoroethyl)phosphonoacetate **11**. EXPERIMENTAL

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#### EXPERIMENTAL

#### GENERAL

Tetrahydrofuran (THF) and benzene were dried by distillation under argon from sodium/benzophenone ketyl just prior to use; triethylamine (TEA) was dried by distillation under argon from calcium hydride; lithium bromide (LiBr, Aldrich Chemical Company, 99+%) was dried in an abderhalden flask over refluxing xylene at 0.3 torr and stored in a desiccator and transferred under argon in a glove bag; diethylether was taken from a freshly opened can of anhydrous ether.

**A**11 reactions were performed under an atmosphere of argon. Infrared spectra were recorded on a Pye-Unicam SP-100 Infrared Spectrometer or a Perkin-Elmer Model 167 Spectrometer with polystyrene as standard. Proton Nuclear Magnetic Resonance Spectra (1H-NMR) were recorded on a in CDCl<sub>3</sub> or on a Bruker WM-250 Varian T-60 at 60 MHz Spectrometer at 250 MHz in CDCl<sub>3</sub>. Chemical shifts are reported in parts per million (& scale) from internal standard tetramethylsilane. Data are reported as followed: chemical shifts (multiplicity: s=singlet, bs=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant (Hz). Electron impact (EI/MS, 70 eV) mass spectra

were recorded on a Finnigan 4000 with an INCOS 4021 data system. Preparative GC operations were performed on a Varian 920 Chromatograph equipped with a 6 ft x 0.25 in stainlesssteel column packed with 15% SE-30 on chromasorb ₩. Qualitative GLPC analyses were performed on a 5880A Hewlett-Packard Gas Chromatograph equipped with a flame ionization detector using helium as carrier gas and a 25 meter capillary column (ID 0.25 nm) liquid-phase GB-1 Column. GC yields were determined using hydrocarbons as internal standards. Flash column chromatography was performed according to the procedure of Still, et. al.44, by using the DAVISIL 62 silica gel mentioned and eluted with the solvents mentioned. The columns outer diameter (o.d.) is listed in millimeters.

## <u>General Procedure for the Preparation of Triethylphosphono-</u> acetate 2.45

257 mL (1.5 mole) of triethylphosphite was added 2 hours) 166.3 mL (1.5 dropwise (over to mole) ethylbromoacetate at 0°C with energetic stirring. The solution stirred for 3 additional hours. Was The ethylbromide was distilled off at low pressure. The crude product triethylphosphonoacetate was purified by distillat ion. bp: 128-130°C (6 torr). 303.5g (90.3%) of pure 2.

<u>General Procedure for the Preparation of Ethyl dichlorophos-</u> phonoacetate 14.

The following procedure is a slight modification of that described by K. A. Petrov.<sup>46</sup> 416g (2 moles) of phosphoruspentachloride were added in portions over 1 hour to 224g (1 mole) of triethlphosphonoacetate with vigorous stirring. The mixture was heated for 5 hours to 115-120°C, then dry sulfur dioxide (generated from sodium bisulfite and sulfuric acid) was passed into the mixture for 20 minutes at room temperature during which a noticeable heat evolution occured. Thionylchloride and phosphorus oxychloride were removed by distillation at atmospheric pressure. The residue was subjected to vacuum distillation to obtain a fraction with a bp: 75-80°C (0.05 torr). 133.6g (65.5%) of pure 14.

<sup>1</sup>H NMR (60 MHz) (CDCl<sub>3</sub>): δ 1.32 (t, J=10Hz, 3H, CH<sub>3</sub>), 3.7 (d, J=22Hz, 2H, P-CH<sub>2</sub>), 4.40 (q, J=10Hz, 2H, CH<sub>2</sub>).

# Preparation of Ethyl, bis(trifluoroethyl)phosphonoacetate

54.4 mL (0.4 mole) of ethyl dichlorophosphonoacetate 14 was dissolved in 480 mL benzene and cooled to 0°C in an ice bath. To this solution, 58.26 mL (0.8 mole) of trifluoroethanol and 105.25 mL triethylamine in 676 mL benzene was added dropwise. After stirring for 1 hour at  $25^{\circ}$ C, the solvent was evaporated and the residue was

filtered. The solid Et<sub>3</sub>N.HCl was washed with ether and the combined ether filtrates were evaporated. Vacuum distillation of the residue gave 53.12g (40%) of pure 11. <sup>1</sup>H NMR (250 MHz) (CDCl<sub>3</sub>):  $\delta$  1.30 (t, J=10Hz, 3H, CH<sub>3</sub>), 3.16 (d, J=22Hz, 2H, P-CH<sub>2</sub>), 4.24 (q, J=10Hz, 2H, CH<sub>2</sub>), 4.47 (p, J=10Hz, 4H, 2CF<sub>3</sub>CH<sub>2</sub>). EI/MS (70 eV): 332 (M, 65.12), 305 (29.07), 287 (base), 260 (29.65), 245 (27.76), 240 (36.87), 161 (20.66), 113 (10.43), 99 (17.13), 83 (33.77), 69 (36.00), 59 (6.40), 47 (23.18), 43 (25.73), 42 (78.20), 33 (62.02).

### <u>General Procedure Used for the Modified HWB Olefination</u> Reaction.<sup>40</sup>

The following procedure is representative of the procedure used to obtain the results described in Table 1. A 50 mL flask with a side arm, a septum inlet and a magnetic stirrer was flame dried under argon. Anhydrous lithium bromide (6 mmol, 0.521g) was weighed in a glove bag and transferred under a stream of argon to the flask. Tetrahydrofuran (10 mL) and ethyl bis(trifluoroethyl)phosphonoacetate (1.177 mL, 5 mmol) were added and the mixture stirred an additional 10 minutes. The carbonyl compound was then added and the reaction mixture stirred overnight at 25°C. After quenching with dilute HCl, the reaction mixture was extracted with ethylether  $(3 \times 10 \text{ mL})$ . The organic extracts were washed with a saturated sodium chloride solution then combined and dried over magnesium sulfate.

<u>General Procedures for the Isolation of the Products  $\alpha$ ,  $\beta$ -Unsaturated Esters.</u>

The combined extracts described above were filtered and the solvent removed *in vacuo*. The methods of purification of the products used were short-path distillation or flash column chromatography.

#### Bthyl Cyclohexylidene Acetate.47

Ethyl cyclohexylidene acetate was prepared from 11 and cyclohexanone and purified by short-path distillation. bp: 50°C (0.2 torr).

<sup>1</sup>H NMR (60 MHz) (CDCl<sub>3</sub>):  $\delta$  1.23 (t, J=7Hz, 3H, CH<sub>3</sub>), 1.62 (m, 6H, 3CH<sub>2</sub>), 2.10 (m, 2H, CH<sub>2</sub>), 2.84 (m, 2H, CH<sub>2</sub>), 4.10 (q, J=7Hz, 2H, CH<sub>2</sub>), 5.60 (bs, 1H, CH=C). IR (neat): 1625 cm<sup>-1</sup> (C=C). EI-MS (70 eV): 168 (M, 91.62), 140 (48.71), 123 (85.27), 80 (75.78), 67 (58.01), 55 (89.59), 41 (base), 39 (91.71).

#### **Bthyl Cyclopentylidene Acetate**. 47

Ethyl cyclopentylidene acetate was prepared from 11 and cyclopentanone and purified by short-path distillation. bp: 93-96°C (20 torr).

<sup>1</sup>H NMR (60 MHz) (CDCl<sub>3</sub>):  $\delta$  1.25 (t, J=7Hz, 3H, CH<sub>3</sub>), 1.70 (m, 4H, 2CH<sub>2</sub>), 2.40 (m, 2H, CH<sub>2</sub>), 2.74 (m, 2H, CH<sub>2</sub>), 4.10 (q, J=7Hz, 2H, CH<sub>2</sub>), 5.76 (m, 1H, CH=C). IR (neat): 1645 cm<sup>-1</sup> (C=C). BI/MS (70 eV): 154 (M, 47.11), 126 (42.62), 109

(64.90), 97 (21.81), 79 (56.31), 69 (14.38), 67 (73.15), 55 (20.44), 53 (46.04), 41 (96.38), 39 (base).

#### <u>Bthyl 3-Bthyl-2-pentenoate.47</u>

Ethyl 3-ethyl-2-pentenoate was prepared from 11 and 3pentanone. The crude product was purified by column chromatography on silica gel (60-200 mesh, 100g, 50 mm o.d., hexane-ether 4:1, 25 mL fractions) using the flash technique.

<sup>1</sup> H NMR (60 MHz) (CDCl<sub>3</sub>):  $\delta$  0.9-1.3 (m, 9H, 3CH<sub>3</sub>), 2.14 (q, J=8Hz, 2H, CH<sub>2</sub>), 2.60 (q, J=8Hz, 2H, CH<sub>2</sub>), 4.10 (q, J=7Hz, 2H, CH<sub>2</sub>), 5.62 (m, 1H, CH=C). IR (neat): 1640 cm<sup>-1</sup> (C=C). EI/MS (70 eV): 156 (M, 46.74), 128 (19.15), 111 (86.02), 99 (53.34), 83 (15.09), 81 (37.69), 69 (33.23), 55 (base), 53 (35.93), 43 (66.90), 41 (69.90), 39 (54.55).

#### **<u>Bthyl Cinnamate</u>**.<sup>47</sup>

Ethyl cinnamate was prepared from 11 and benzaldehyde. The crude product was purified by column chromatography on a column of silica gel (60-200 mesh, 100g, 50 mm o.d., hexaneether 4:1, 25 mL fractions) using the flash technique. A mixture of E and Z isomers was obtained; the ratio was determined by GC analysis. Found: 44:56 E/Z ratio.

<sup>1</sup>H NMR (250 MHz) spectrum of mixture and assignments (based on literature values of E isomer):  $\delta$  1.22 (t, J=7Hz, CH<sub>3</sub> for Z isomer), 1.32 (t, J=7Hz, 3H, CH<sub>3</sub> for E isomer), 4.15 (q, J=7Hz, 2H, CH<sub>2</sub> for Z isomer), 4.25 (q, J=7Hz, 2H, CH<sub>2</sub> for E

isomer), 5.95 (d, J=12Hz, 1H, CH=C for Z isomer), 6.43 (d, J=16Hz, 1H, CH=C for B isomer), 6.90 (d, J=12Hz, 1H, CH=C for Z isomer), 7.30 (m, 5H, aromatic for E isomer), 7.55 (m, 5H, aromatic for Z isomer), 7.68 (d, J=16Hz, 1H, CH=C for E isomer). IR (neat): 1630 cm<sup>-1</sup> (C=C). EI/MS (70 eV): 176 (M, 30.83), 148 (13.89), 131 (base), 103 (50.76), 77 (48.31), 51 (39.10), 43 (6.80), 39 (11.42).

#### <u>Bthyl 3-Phenyl-2-butenoate.47</u>

Bthyl 3-phenyl-2-butenoate was prepared from 11 and acetophenone. A pure sample of the B isomer was obtained by preparative GC.

<sup>1</sup>H NMR (E isomer) (60 MHz) (CDCl<sub>3</sub>):  $\delta$  1.24 (bs, 3H, CH<sub>3</sub>), 2.50 (bs, 3H, CH<sub>3</sub>), 4.10 (q, J=7Hz, 2H, CH<sub>2</sub>), 6.04 (m, 1H, CH=C), 7.24 (m, 5H, aromatic). IR (neat): 1625 cm<sup>-1</sup> (C=C). EI/MS (70 eV): 190 (M, 52.69), 161 (37.58), 145 (base), 117 (49.38), 115 (92.44), 102 (11.59), 91 (43.63), 51 (28.16), 39 (28.52).

#### <u>Bthyl 3,3-Diphenyl-2-propenoate</u>.

Bthyl 3,3-diphenyl-2-propenoate was prepared from 11 and benzophenone. A pure sample was obtained by preparative GC.

<sup>1</sup> H NMR (60 MHz) (CDCl<sub>3</sub>):  $\delta$  1.28 (t, J=7Hz, 3H, CH<sub>3</sub>), 4.06 (q, J=7Hz, 2H, CH<sub>2</sub>), 6.38 (s, 1H, CH=C), 7.31 (s, 10H, aromatic). EI/MS (70 eV): 252 (M, 46.29), 251 (15.22), 223 (15.96), 207 (base), 180 (50.28), 179 (72.02), 152 (18.99),

105 (40.45),102 (12.92),89 (19.02), 77 (31.97), 51 (35.96), 43 (12.84).

Reaction of Cyclohexanone With 11 in the Presence of Lithium Diisopropylamine.

A 50 mL flask with a side arm, a septum inlet and a magnetic stirrer was flame dried under argon. THF and diisopropylamine (0.7 mL, 5 mmol) were added, the mixture was stirred 5 minutes at 0°C, then n-butyllithium (3.125 mL, 5 mmol) was added and the solution was stirred for t<sub>1</sub> at T<sub>1</sub>. 11 (1.177 mL, 5 mmol) was added and the mixture was cooled to  $-78^{\circ}$ C and stirred for 15 minutes. Cyclohexanone (0.52 mL, 5 mmol) was added at  $-78^{\circ}$ C and the mixture stirred for 15 minutes at  $-78^{\circ}$ C then warmed to T<sub>2</sub> and stirred for t<sub>2</sub>. After quenching with dilute HCl, the mixture was analyzed by GC for product presence.

\* 5 minutes at 25°C in a water bath. Triethylamine (6 mmol,
0.83 mL) was added and the mixture

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