Pergamon

Tetrahedron Vol. 51, No. 6, pp. 1721-1740, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)01046-3

Horner-Wadsworth-Emmons Olefination of Nonstabilized Phosphonates. A New Synthetic Approach to β,γ-Unsaturated Amides.

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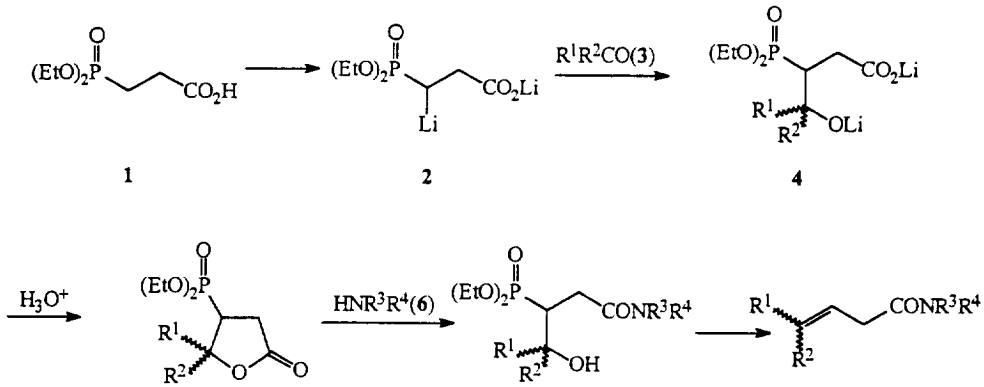
Abstract: Aminolysis of readily accessible β-diethoxyphosphonyl-γ-butyrolactones **5** and **22** provides a convenient entry to (E)-β,γ-unsaturated amides **8** and **24** respectively. The key step of the aminolysis involves elimination of diethoxyphosporic acid from the corresponding β-hydroxyalkylphosphonates **7** and **23**. Stereochemistry of the amides **8** and **24** results from their consecutive base catalyzed isomerization.

INTRODUCTION

In contrary to alkylphosphonates bearing carbanion stabilizing groups on the α-carbon, nonstabilized alkylphosphonates are in general insufficiently reactive partners of aldehydes and ketones to undergo spontaneous Horner-Wadsworth-Emmons olefination. Although base promoted addition of nonstabilized alkylphosphonates to carbonyl compounds is usually efficient and results in the formation of β-hydroxyalkylphosphonates, further decomposition of these intermediates to produce olefins requires specific catalysis. It has been reported that some β-hydroxyalkylphosphonates which lack α electron-withdrawing groups can be converted into corresponding olefins by the agency of either cesium fluoride or potassium carbonate[1].

We have recently demonstrated that employing selected primary and secondary amines as the olefination catalysts is equally effective and that it opens up attractive possibilities for a new synthesis of β,γ-unsaturated amides **8**[2]. When dilithium β-diethoxyphosphorylpropionate **2** was allowed to react with aldehydes or ketones **3**, the respective β-diethoxyphosphorylbutyrolactones **5** were obtained as sole products and no olefination was observed. However, heating **5** in the presence of amines **6** resulted in decyclization of the lactone ring to give β-hydroxyalkylphosphonates **7**, which subsequently eliminated

elements of diethylphosphoric acid affording the amides **8**. Surprisingly, we found that both stereoisomeric lactones cis-**5** and trans-**5** are converted into the amides **8** of E-configuration. Such a stereochemical outcome is inconsistent with the expected tendency of threo- and erythro-β-hydroxyalkylphosphonates, which do not contain α electron-withdrawing substituents to undergo stereospecific elimination producing E- and Z-olefins respectively[3].



1 **2** **4**

5 **7** **8**

In this paper we unequivocally elucidated the "unusual" stereochemistry and successfully extended the synthetic utility of a new stepwise Horner-Wadsworth-Emmons approach to the amides **8**.

RESULTS AND DISCUSSION

The acid **1** is easily converted into the dilithium salt **2** by a standard treatment with two equivalents of LDA in THF solution. The reaction occurs regiospecifically, and no signs of dilithiation involving carboxyl functionality and the adjacent methylene group is observed. Addition of the selected aldehyde or ketone **3** to the salt **2** provides exclusively lactones **5** as mixtures of trans- and cis- isomers in satisfactory yields (Table 1). Some of these mixtures were separated by using silica gel column chromatography.

Configurational assignments for the lactones **5** were troublesome. $^3J_{PH}{}^5$ Coupling constants successfully used as a convenient configurational criterion for the phosphine oxide **9** and its homologues[4], which structurally and stereochemically remind the lactones **5**, were either very similar for both isomers or were undeterminable. For the same reasons $^3J_{H}{}^4{}_{H}{}^5$ had no diagnostic meaning as well.

In this situation we turned our attention to the less deceptive spectral data. ^{1}H NMR Spectra of the lactones **5c** and **5d** bearing aromatic substituents revealed that protons of the ethoxy group in the

Table 1. Lactones **5** Prepared

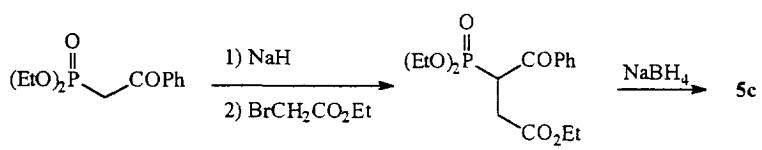
5	R^1	R^2	Yield[a] (%)	trans/cis[b]
a	Me	H	45	85/15
b	i-Pr	H	62	85/15
c	Ph	H	55	60/40
d	4-$NO_2C_6H_4$	H	63	65/35
e	Ph CH=CH	H	70	65/35
f	Me	Me	32	-

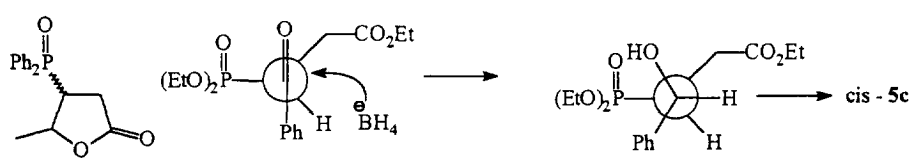
a) Yield of isolated product based on **1**

b) Taken from ^{31}P NMR data of the crude product

minor isomer are shifted upfield when compared with the major one, eg. 1.01 ppm and 1.25 ppm for **5c**. We attributed this shift to the shielding effect of a benzene ring exerted on the protons of the cis oriented diethoxyphosphoryl group. To confirm such an assignment, the lactone **5c** was synthesized using an independent method, which is known to give structurally similar lactone cis-**9** predominantly[4].

Thus, routine alkylation of the ketone **10** with ethyl bromoacetate, in the conditions usually employed in this type of reactions, gave the ketone **11**. Standard reduction of **11** with $NaBH_4$, yielded the lactone **5c** as a mixture of diastereoisomers in 80:20 ratio. Configuration of the major isomer could be predicted by analysis of the Felkin's model **12**. Stereochemically favoured approach of borohydride

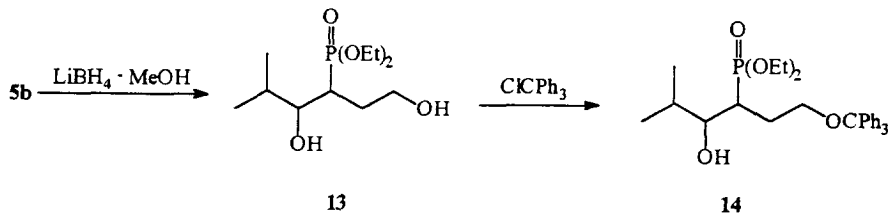




to the less hindered face of the ketone **11** should give the lactone cis-**5c** predominantly. Since major isomer obtained this way and minor isomer of **5c** obtained from the acid **1** had identical spectral characteristics, it was evident that the latter had cis configuration as well. This conclusion and the observed shielding effect of the benzene ring both indicate that major isomers of the lactones **5c** and **5d** have trans configuration.

Predominating isomers of the lactones **5a,b,e** bearing alkyl substituents seemed also to have trans configuration. ^{1}H NMR spectrum of the major isomer of **5e** revealed the same shielding effect of the benzene ring as observed for, **5c** and **5d**, and the signals of the major isomers of **5a,b,e** in their ^{31}P NMR spectra showed the same downfield shift as did lactones trans-**5c,d**.

However final assignment was made by x-ray analysis. Major isomer of the lactone **5b** was reduced to the diol **13**, using $LiBH_4$-MeOH system[5]. Chemoselective reaction of **13** with trityl chloride in the standard conditions gave fine crystals of the alcohol **14** that were suitable for x-ray analysis.



13 **14**

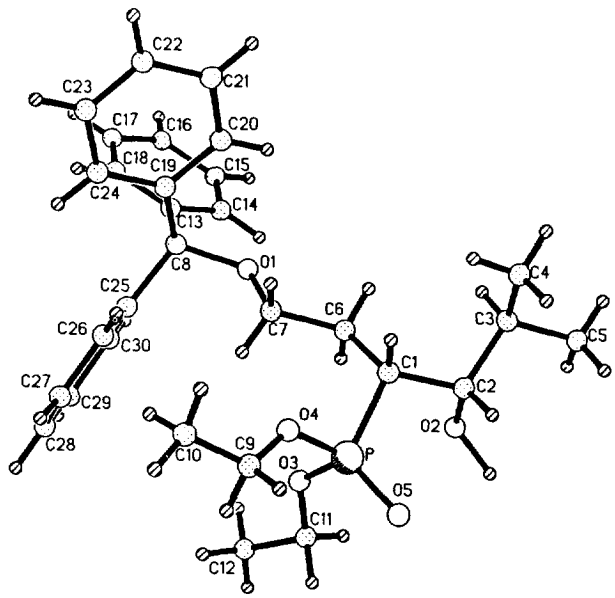


Fig. X-Ray Structure of **14**

The X-ray analysis unequivocally showed[6] that the crystals were (1R*, 2S*)-diethyl 2-hydroxy-3-methyl-1-(2-triphenylmethoxyethyl)butylphosphonate (**14**) (Figure) and consequently, that the major diastereoisomer of the lactone **5b** had trans configuration.

Presented results demonstrate that trans lactones **5a-e** are predominantly formed in the reaction of the acid **1** with both aliphatic and aromatic aldehydes. However, higher stereoselectivity is observed for the reaction with the former.

The lactones **5** heated in boiling xylene with primary or secondary amines **6** for 8 and 15 h respectively gave, after aqueous work up, the expected β,γ-unsaturated amides **8** in good to very good yield (Table 2). Crude products were purified by column chromatography on silica gel.

Table 2. β,γ-Unsaturated Amides **8** Prepared.

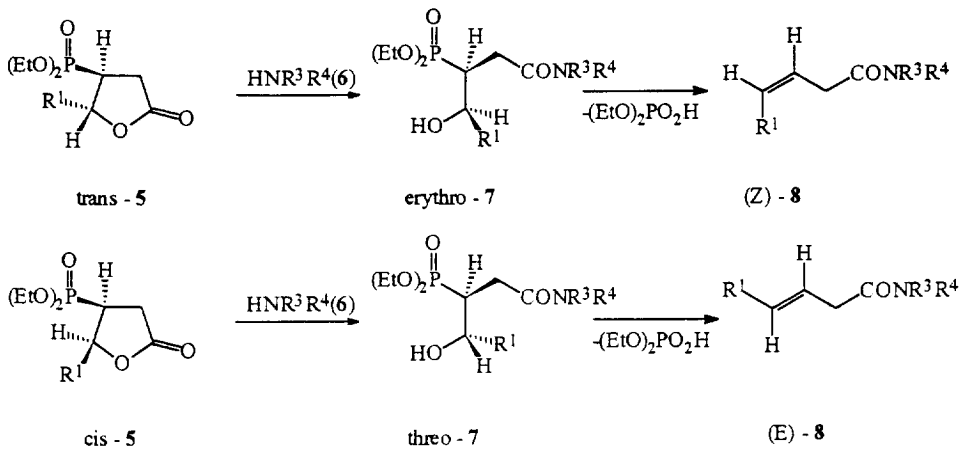
8	R^1	R^2	R^3	R^4	Substrate	Reaction time (h)	Yield[a] (%)	E/Z[b]
a	Me	H	$CH(CH_3)Ph$	H	**5a**	8	75	85/15
b	i-Pr	H	$CH(CH_3)Ph$	H	**5b**	8	73	>95/5
c	i-Pr	H	$CH_2CH_2OCH_2CH_2$		**5b**	15	62	>95/5
d	i-Pr	H	$CH_2(CH_2)_3CH_2$		**5b**	15	59	>95/5
e	Ph	H	$CH(CH_3)Ph$	H	**5c**	8	76	>95/5
f	$4NO_2C_6H_4$	H	$CH(CH_3)Ph$	H	**5d**	8	79	>95/5
g	PhCH=CH	H	$CH(CH_3)Ph$	H	**5e**	8	53	>95/5
h	Me	Me	$CH(CH_3)Ph$	H	**5f**	8	65	-

a) Yield of isolated product based on 5.

b) Taken from ^1H NMR data of the crude product.

All amides **8** had a double bond in β-position, and all but one were obtained as individual E-isomers. Regio- and stereo-chemistry of **8** were unequivocally assigned by the diagnostic chemical shifts and multiplicity of the signals of both α and olefinic protons in their ^1H NMR spectra, e.g.; for **8b**, as expected, α protons show up as doublet at $\delta=2.89$, and olefinic protons appear as double triplet (H_β) and double doublet (H_γ) at $\delta=5.47$ and $\delta=5.56$ respectively, with coupling constant $J(H_\beta H_\gamma)=15.5$ Hz.

As was mentioned in the introduction, the stereochemical outcome of these reactions was

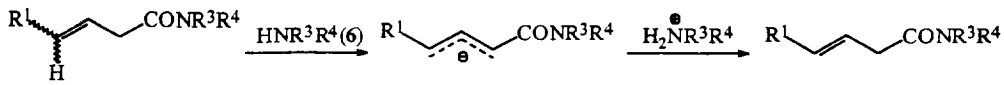


Scheme

inconsistent with our anticipation that decyclization of the lactones trans-**5** and cis-**5** and subsequent syn elimination of the diethylphosphoric acid from the corresponding erythro- and threo-β-hydroxyalkylphosphonates **7** should produce olefines **8** of Z and E configuration respectively (Scheme). In our experiments all amides **8** (except **8a**) have been obtained as individual E-isomers regardless of the configuration of the starting **5**, e.g., trans-**5b** yielded E-**8b** exclusively; cis-**5d** and trans-**5d**, reacted individually, both gave E-**8f** as the only product.

The observed "unusual" stereochemistry can be rationalized by assuming either an easy interconversion of the erythro-7 and threo-7 occurring under the reaction conditions or E/Z isomerization of the final β,γ-unsaturated amides **8**. However, synthesis of homologous γ,δ-unsaturated amides following similar reaction sequence, and starting from γ-diethoxyphosphorylbutyric acid, gave always mixtures of E and Z olefines, in some cases with the latter even predominating[7]. This observation suggests that no interconversion between homologous erythro- and threo β-hydroxyalkylphosphonates takes place when they are exposed to the same conditions as **7**.

In this situation we focused our attention on the E/Z isomerization of the amides **8** . Such an isomerization can be easily completed by the amine promoted deprotonation-protonation mechanism, via the anions **15a-g**. However, formation of the anions **15a-g** should have induced not only E/Z but also $\alpha,\beta \rightleftarrows \beta,\gamma$ isomerization of the double bond to produce substantial amount of the conjugated α,β-unsaturated amides. This should have been in particular the case for the amides **8a-d** bearing alkyl substituents unable to stabilize effectively β,γ-position of the double bond[8].



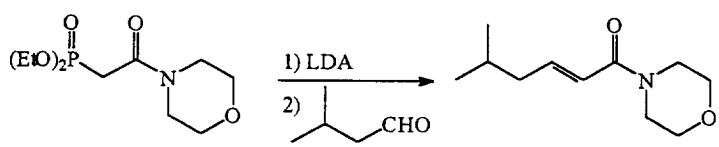
8a-g **15a-g** **(E)-8a-g**

The only evidence proving the formation of α,β-unsaturated amides was found in the ^{1}H NMR spectrum of the crude **8c**, where weak signals consistent with the structure of the amide **16** were present. Particularly indicative were three double triplets at δ=2.11 (CH_2 in γ position), δ=6.20 (H_α), and δ=6.89 (H_β).

Reasonable explanation of the observed regiochemistry emerged from the fact that kinetically controlled alkylations and protonations of the anions similar to **15** occurred exclusively on the α-carbon to give deconjugated products[9]. The conditions employed in the aminolyses of the lactones **5** (reflux in xylene, 8-15 h) did not seem to favor the kinetic control of the regiochemistry of the final products. However, α-protonation of **15** much faster than its γ-protonation could significantly delay $\alpha,\beta \rightleftarrows \beta,\gamma$ isomerization.

In order to verify this hypothesis the following experiments proving the structure of the amide **16** and providing detail information about $\alpha,\beta \rightleftarrows \beta,\gamma$ isomerisations of the alkyl substituted amides **8b** and **8c** were performed.

a) The amide **16** was routinely synthesized using Horner-Wadsworth-Emmons olefination of isovaleryl aldehyde with 4-(2-diethoxyphosphoryl-1-oxoethyl)morpholine (**17**). ^{1}H NMR Signals of **16** obtained this way were identical with the weak signals present in the spectrum of the crude **8c**.

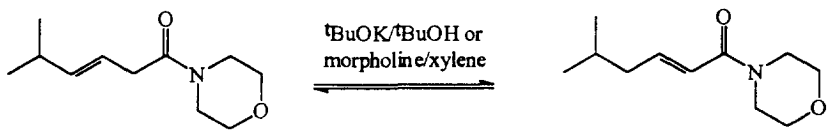


17 **16**

b) The amide (E)-**8c** was treated with ^{t}BuOK/^{t}BuOH solution at room temperature for five days and, after this time, ^{1}H NMR spectrum of the product revealed the presence of both (E)-**8c** and **16** in the ratio 20:80 respectively. Longer reaction time has not changed this proportion. The ratio was easily determined from the integration of the well resolved signals of α-methylene protons of (E)-**8c** (δ=3.08) and γ-methylene protons of **16** (δ=2.11).

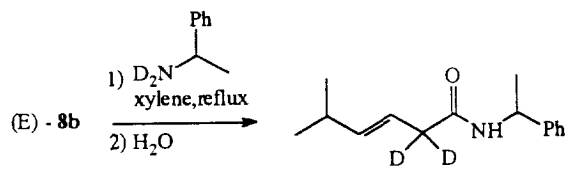
c) The amide (E)-**8c** was heated under reflux with morpholine in xylene for 15 h to give the mixture of (E)-**8c** and **16** in the ratio 95:5 respectively, as estimated by ^{1}H NMR. Further heating of

the reaction mixture for 80 h afforded a mixture of (E)-**8c**:**16** in the ratio 75:25.



(E)-**8c** **16**

d) The amide (E)-**8b** was heated under reflux with excess of phenylethyl(D_2)amine in xylene for 8 h. The obtained product **18** had deuterium incorporated exclusively in the α-position. The degree of deuteration was 90%.



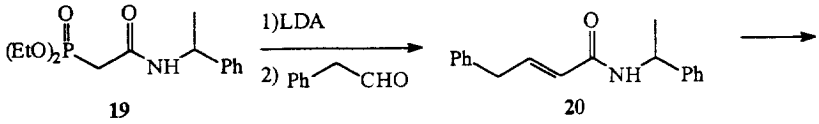
18

Several conclusions may be drawn from these results, all in favor of our hypothesis. In tBuOK/tBuOH the equilibrium mixture of (E)-**8c** and **16** can be easily obtained at room temperature [(E)-**8c**:**16** = 20:80, experiment b]. However, the equilibrium between (E)-**8c** and **16** is much more difficult to accomplish in the presence of amine in refluxing xylene. In the latter case even heating under reflux for 80 h gives the mixture of (E)-**8c** an **16** which is far from the equilibrium (experiment c). Incorporation of deuterium in the α-position and the absence, at the same time, of the detectable amount of deuterium in the γ-position of **18** (experiment d) proves that the rate of α-deuteration is much faster than γ-deuteration.

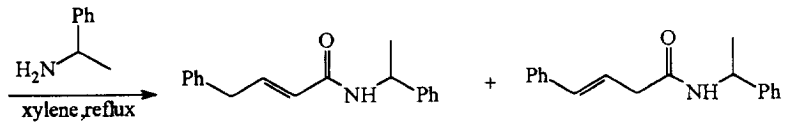
Summarizing we found that the observed stereochemistry and regiochemistry of the amides **8a-d** was controlled by thermodynamic and kinetic factors respectively. The full thermodynamic control can be achieved either by prolonged reaction time or by using a stronger base. We believe this is true for all amides **8** substituted with alkyl group (R^1=alkyl). It is noteworthy that the observed phenomenon is unique among the reports dealing with $\alpha,\beta \rightleftarrows \beta,\gamma$ isomerizations of unsaturated carbonyl compounds, and also gives apparent synthetic advantage, as less stable β,γ-unsaturated amides can be isolated in a pure form.

Contrary to the alkyl substituted β,γ-unsaturated amides **8a-d**, the amides **8e-h** bearing electron-withdrawing substituents proved to be thermodynamically more stable than their α,β-unsaturated isomers. When α,β-unsaturated amide **20** obtained from diethoxyphosphoryl-N-(1-phenylethyl)acetamide

(**19**) and phenylacetaldehyde was allowed to react with 1-phenylethylamine in refluxing xylene for 8 h, a 95:5 mixture of **8e** and **20** was obtained, as estimated from ^{1}H NMR spectrum. Thus, the regio- and stereo-chemistry of the amides **8e-h** are both the result of the thermodynamic control.

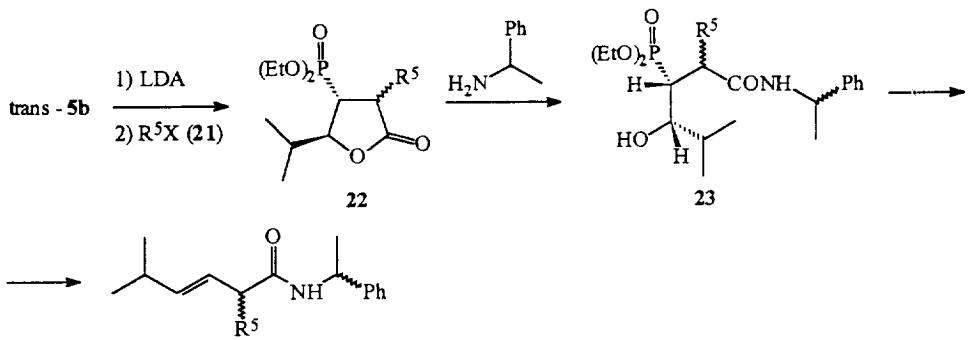


19 **20**



20 (5%) **8e** (95%)

An interesting extension of our approach to β,γ-unsaturated amides was accomplished by additional alkylation of the lactones **5**. Thus, standard alkylation of trans-**5b** with alkyl or allyl halides **21** gave, after aqueous work up and purification by column chromatography on silica gel, α-substituted lactones **22** in a good yield. Most of the lactones **22** were formed as single isomers. Only the lactone **22a** was obtained as 90:10 mixture of diastereoisomers (Table 3).

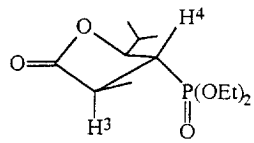


22 **23**

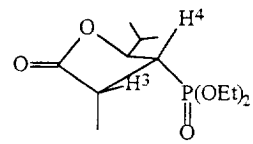
24

Stereochemistry of the lactones **22** including both stereoisomers of **22a** was assigned on the ground of their ^{1}H NMR spectra. $^3J_{H^3H^4}$ coupling constants observed for major and minor isomers of **22a** (10.2 Hz and 7.4 Hz respectively) indicate the trans relation of these protons in the former. The configurational models with phosphoryl and isopropyl groups in pseudo equatorial positions display $H^3C\text{-}CH^4$ torsion angles of 160-170° for **22a'** and 40-50° for **22a''**. Carplus equation gives J=9-11 Hz for an angle of 160-170° and J=6-8 Hz for one of 40-50°. The observed $^3J_{H^3H^4}$ coupling constants are

consistent with the above predictions. $^{3}J_{PCCH}{}^{3}$ coupling constants of major and minor isomers (19.3 Hz and 1.7 Hz respectively) also confirm such an assignment. The appropriate torsion angles taken from models are 40-50° for **22a'** and 80-90° for **22a''**, the values corresponding to $^{3}J_{PCCH}{}^{3}$ = 9-12 Hz and 0-2 Hz respectively as calculated from the Benezra's equation [10].



22a'



22a''

Thus stereoselective alkylation of the lithium enolate derived from trans-**5b** to give lactones **22a-d** is best explained by approach of alkyl or allyl halide **21** to the less hindered side of the lactone ring, i.e. anti to the large, adjacent phosphoryl group.

Table 3. Lactones **22a-d** and β,γ-Unsaturated Amides **24a-d** Prepared.

22,24	R^5 X(**21**)	**22** Ratio of isomers[a]	**22** Yield[b] (%)	Reaction time (h)	**24** Yield[b] (%)
a	MeJ	90/10	65	15	70
b	EtJ	>95/5	40	20	60
c	CH_2=CH-CH_2Br	>95/5	55	20	65
d	CH_2=CBr-CH_2Br	>95/5	45	20	55

a) Taken from ^{31}P NMR data of the crude product.

b) Yield of isolated product based, on trans-**5b** or **22** respectively.

Treatment of the lactones **22** with 1-phenylethylamine under the conditions similar to those used for the lactones **5** gave the expected α-substituted β,γ-unsaturated amides **24** in a satisfactory yield (Table 3). β-Position and E configuration of the double bond in **24** were confirmed by characteristic chemical shifts and coupling constants in their ^{1}H NMR spectra, similar to those recorded for the amides **8**. As expected, ^{1}H NMR spectra also revealed, that each amide **24** is a mixture of two diastereoisomers in the ratio 1:1.

In summary, we have developed a general method for the stereoselective synthesis of (E)-β,γ-unsaturated amides **8** and **24** based on a novel, stepwise Horner-Wadsworth-Emmons olefination of carbonyl compounds using β-diethoxyphosphorylpropionic acid **1**. Easy access to the starting **1**, as well as wide scope and preparative simplicity make this procedure especially convenient. Additionally we have elucidated the nature of the unexpected (Z)→(E) isomerization of the amides **8** and **24** proceeding in the olefination conditions.

EXPERIMENTAL

Reagents and solvents were purified in the usual way. Melting points were determined on a Büchi SMP-20 instrument and are uncorrected. ^{1}H NMR spectra were recorded on a Tesla BS 587A, Bruker MSL-300 or General Electric GM 500 spectrometer at 80 MHz, 300 MHz, and 500 MHz respectively, using TMS as internal standard. ^{31}P NMR spectra were taken on a Bruker HFX-72 at 36.43 MHz with 85% H_3PO_4 as external standard, utilizing broad band proton decoupling. LDA was prepared from BuLi in hexanes. All reactions requiring anhydrous conditions were conducted under an argon atmosphere. β-Diethoxyphosphorylpropionic acid (**1**),[11] diethyl (2-oxo-2-phenylethyl)phosphonate (**10**)[12] and diethoxyphosphorylacetyl chloride[13] were obtained according to the literature procedures. 1-Phenylethyl(D_2)amine was obtained from 1-phenylethylamine and D_2O as described in the literature.[14] The degree of deuteration determined by ^{1}H NMR spectroscopy was more then 95%.

*Preparation of the lactones **5a-f**. General procedure.*
A solution of the acid **1** (2.1 g, 10 mmol) in THF (10 mL) was added at -70°C to a solution of LDA (22 mmol) in THF (20 mL). The reaction mixture was maintained at -20°C for 1 h, and then carbonyl compound **3** (20 mmol) in THF (20 mL) was added at -70°C. After stirring for 2 h at room temperature water (30 mL) was added. The aqueous layer was washed with Et_2O (2x20 mL), acidified to pH 1 with 10% HCl solution and extracted with $CHCl_3$ (4x30 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL), dried and the solvent was removed to give crude isomeric lactones **5** which were purified and separated (for lactones **5b-d**) by column chromatography (silica gel, EtOAc/MeOH, 9.5:0.5 as eluent).

*4-Diethoxyphosphoryl-4,5-dihydro-5-methyl-2(3H)-furanone (**5a**).* Oil; ^{1}H NMR[15] ($CDCl_3$) *trans*-**5a** δ 1.36 (t, J=7.0 Hz, 6H), 1.52 (d, J=6.0 Hz, 3H), 2.45 (dddd, J=19.3, 10.8, 9.0, 8.5 Hz, 1H), 2.70-2.96 (m, 2H), 4.08-4.26 (m, 4H), 4.74 (ddq, J=11.7, 8.5, 6.0 Hz, 1H); *cis*-**5a** δ 1.36 (t, J=7.0 Hz, 6H), 1.55 (d, J=6.5 Hz, 3H), 2.40-2.55 (m, 1H), 2.70-2.96 (m, 2H), 4.08-4.26 (m, 4H), 4.88 (ddq, J=10.2, 7.2, 6.5 Hz, 1H); ^{31}P NMR[15] ($CHCl_3$) *trans*-**5a** δ 25.18; *cis*-**5a** δ 24.27. Anal. Calcd for $C_9H_{17}O_5P$: C, 45.76; H, 7.26; P, 13.11. Found: C, 45.51; H, 7.22; P, 12.91.

*trans-4-Diethoxyphosphoryl-4,5-dihydro-5-isopropyl-2(3H)-furanone trans-(**5b**).* Oil; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J=6.6 Hz, 3H), 1.04 (d, J=6.6 Hz, 3H), 1.35 (t, J=7.0 Hz, 6H), 1.97 (d heptet, J=4.8, 6.6 Hz, 1H), 2.60 (dddd, J=15.0, 9.7, 7.6, 5.7 Hz, 1H), 2.71-2.84 (m, 2H), 4.10-4.25 (m, 4H), 4.55 (ddd, J=15.9, 5.7, 4.8 Hz, 1H); ^{31}P NMR ($CHCl_3$) δ 26.68. Anal. Calcd for $C_{11}H_{21}O_5P$: C, 49.99; H, 8.01; P, 11.72. Found: C, 50.22; H, 8.13; P, 11.51.

*cis-4-Diethoxyphosphoryl-4,5-dihydro-5-isopropyl-2(3H)-furanonecis-(**5b**).* Oil; ^{1}HNMR ($CDCl_3$) δ 1.07 (d, J=6.5 Hz, 3H), 1.09 (d, J=6.5 Hz, 3H), 1.27 (t, J=7.0 Hz, 6H), 2.25 (octet, J=6.5 Hz, 1H), 2.61-2.90 (m, 3H), 4.01-4.35 (m, 5H); ^{31}P NMR ($CHCl_3$) δ 24.61. Anal. Calcd for $C_{11}H_{21}O_5P$: C, 49.99; H, 8.01; P, 11.72. Found: C, 50.31; H, 8.33; P, 11.98.

*trans-4-Diethoxyphosphoryl-4,5-dihydro-5-phenyl-2(3H)-furanone trans-(**5c**).* Oil; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J=7.0 Hz, 6H), 2.78-3.01 (m, 3H), 3.97-4.19 (m, 4H), 5.63 (dd, J=12.8, 7.5 Hz, 1H), 7.35-7.45 (m, 5H); ^{31}P NMR ($CHCl_3$) δ 24.98. Anal. Calcd for $C_{14}H_{19}O_5P$: C, 56.37; H, 6.42; P, 10.38. Found: C, 56.19; H, 6.38; P, 10.53.

*cis-4-Diethoxyphosphoryl-4,5-dihydro-5-phenyl-2(3H)-furanone cis-(**5c**).* Oil; ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J=7.0 Hz, 3H), 1.17 (t, J=7.0 Hz, 3H), 2.75-3.09 (m, 2H), 3.23-3.95 (m, 5H), 5.80 (dd, J=11.5, 8.0 Hz, 1H), 7.30-7.47 (m, 5H); ^{31}P NMR ($CHCl_3$) δ 22.60. Anal Calcd for $C_{14}H_{19}O_5P$: C, 56.37; H, 6.42; P, 10.38. Found: C, 56.07; H, 6.21; P, 10.29.

*trans-4-Diethoxyphosphoryl-4,5-dihydro-5-(4-nitrophenyl)-2(3H)-furanone trans-(**5d**).* Oil; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J=7.0 Hz, 3H), 1.29 (t, J=7.0 Hz, 3H), 2.76 (dddd, J=15.3, 10.1, 8.7, 7.2 Hz, 1H), 2.84-3.02 (m, 2H), 4.05-4.21 (m, 4H), 5.71 (dd, J=13.6, 7.2 Hz, 1H), 7.59 (d, J=9.0 Hz, 2H), 8.23 (d, J=9.0 Hz, 2H); ^{31}P NMR ($CHCl_3$) δ 23.81. Anal. Calcd for $C_{14}H_{18}NO_7P$: C, 48.98; H, 5.28; N, 4.08; P, 9.02. Found: C, 48.87; H, 5.22; N, 4.25; P, 9.30.

*cis-4-Diethoxyphosphoryl-4,5-dihydro-5-(4-nitrophenyl)-2(3H)-furanone cis-(**5d**).* Oil; ^{1}H NMR ($CDCl_3$) δ 1.04 (t, J=7.0 Hz, 3H), 1.19 (t, J=7.0 Hz, 3H), 2.82-3.09 (m, 2H), 3.20-3.97 (m, 5H), 5.81 (dd, J=15.8, 7.5 Hz, 1H), 7.54 (d, J=8.5 Hz, 2H), 8.24 (d, J=8.5 Hz, 2H); ^{31}P NMR ($CHCl_3$) δ 21.89. Anal. Calcd for $C_{14}H_{18}NO_7P$: C, 48.98; H, 5.28; N, 4.08; P, 9.02. Found: C, 48.73; H, 5.35; N, 4.02; P, 9.36.

*4-Diethoxyphosphoryl-4,5-dihydro-5-[(E)-2-phenylvinyl]-2(3H)-furanone (**5e**).* Oil; ^{1}H NMR[15] ($CDCl_3$) *trans*-**5e** δ 1.24 (t, J=7.0 Hz, 6H), 2.55-3.22 (m, 3H), 3.85-4.35 (m, 4H), 5.00-5.47 (m, 1H), 6.18 (dd, J=16.0, 6.0 Hz, 1H), 6.74 (d, J=16.0 Hz, 1H), 7.19-7.52 (m, 5H); *cis*-**5e** δ 1.15 (t, J=7.0 Hz, 3H), 1.19 (t, J=7.0 Hz, 3H), 2.55-3.22 (m, 3H), 3.85-4.35 (m, 4H), 5.00-5.47 (m, 1H), 6.37 (dd,

J=16.0, 6.0 Hz, 1H), 6.69 (d, J=16.0 Hz, 1H), 7.19-7.52 (m, 5H); ^{31}P NMR[15] ($CHCl_3$) *trans*-**5e** δ 25.45; *cis*-**5e** δ 24.00. Anal. Calcd for $C_{16}H_{21}O_5P$: C, 59.25; H, 6.53; P, 9.55. Found: C, 59.29; H, 6.41; P, 9.74.

*4-Diethoxyphosphoryl-4,5-dihydro-5,5-dimethyl-2(3H)-furanone (**5f**).* Oil; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, J=7.0 Hz, 3H), 1.37 (t, J=7.0 Hz, 3H), 1.51 (s, 3H), 1.59 (s, 3H), 2.55-3.04 (m, 3H); 4.09-4.30 (m, 4H); ^{31}P NMR ($CHCl_3$) δ 23.57. Anal. Calcd for $C_{10}H_{19}O_5P$: C, 48.00; H, 7.65; P, 12.38. Found: C, 48.08; H, 7.72; P, 12.14.

*Preparation of the amides **8a-h**. General procedure.*

A mixture of the lactone **5** (2.0 mmol) and amine **6** (4.1 mmol) in xylene (10 mL) was heated under reflux for the period of time given in the Table 2. The resultant mixture was cooled to room temperature, washed with 5% aqueous HCl solution (10 mL) and the aqueous layer was extracted with $CHCl_3$ (2x10 mL). The combined organic layers were dried and solvent was evaporated to yield the crude amides **8a-h** which were purified by column chromatography (silica gel, EtOAc/MeOH, 9.5:0.5, as eluent).

*N-(1-Phenylethyl)-3-pentenamide (**8a**).* Oil; ^{1}H NMR[15] ($CDCl_3$) (E)-**8a**: δ 1.39 (d, J=7.0 Hz, 3H), 1.61-1.66 (m, 3H), 2.82-2.87 (m, 2H), 5.04 (quint, J=7.0 Hz, 1H), 5.47 (dtq, J=15.5, 6.0, 1.0 Hz, 1H), 5.54 (dq, J=15.5, 6.0 Hz, 1H), 5.94 (bd, J=7.0 Hz, 1H), 7.14-7.29 (m, 5H); (Z)-**8a**: δ 1.38 (d, J=7.0 Hz, 3H), 1.54-1.59 (m, 3H), 2.92-2.97 (m, 2H), 5.04 (quint, J=7.0 Hz, 1H), 5.63 (dqt, J=11.0, 7.0, 1.0 Hz, 1H), 5.73 (dtq, J=11.0, 7.0, 1.0 Hz, 1H), 5.94 (bd, J=7.0 Hz, 1H), 7.14-7.29 (m, 5H). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.62; H, 8.54; N, 6.69.

*(E)-5-Methyl-N-(1-phenylethyl)-3-hexenamide (E)-(**8b**).* Oil; ^{1}H NMR ($CDCl_3$) δ 0.97 (d, J=6.5 Hz, 6H), 1.44 (d, J=7.0 Hz, 3H), 2.28 (octet, J=6.5 Hz, 1H), 2.89 (d, J=6.0 Hz, 2H), 5.10 (quint, J=7.0 Hz, 1H), 5.47 (dt, J=15.5, 6.0 Hz, 1H), 5.56 (dd, J=15.5, 6.5 Hz, 1H), 6.38 (bd, J=7.0 Hz, 1H), 7.19-7.38 (m, 5H). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.06. Found: C, 77.69; H, 9.20; N, 6.17.

*(E)-4-(5-Methyl-1-oxo-3-hexenyl)morpholine (E)-(**8c**).* Oil; ^{1}H NMR ($CDCl_3$) δ 0.98 (d, J=7.0 Hz, 6H), 2.26-2.37 (m, 1H), 3.08 (d, J=5.0 Hz, 2H), 3.41-3.48 (m, 2H), 3.57-3.63 (m, 6H), 5.48 (dt, J=15.5, 5.0 Hz, 1H), 5.52 (dd, J=15.5, 5.2 Hz, 1H). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.81; H, 9.92; N, 7.21.

*(E)-1-(5-Methyl-1-oxo-3-hexenyl)piperidine (E)-(**8d**).* Oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J=6.5 Hz, 6H), 1.32-1.67 (m ,6H), 2.00-2.35 (m, 1H), 2.92-3.09 (m, 2H), 3.17-3.65 (m, 4H), 5.30-5.49 (m,

2H). Anal. Calcd for $C_{12}H_{21}NO$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.83; H, 10.60; N, 7.01.

*(E)-4-Phenyl-N-(1-phenylethyl)-3-butenamide (E)-(**8e**).* M.p. 94-95°C (Et_2O/hexane); ^1H NMR ($CDCl_3$) δ 1.49 (d, J=7.0 Hz, 3H), 3.16 (d, J=7.0 Hz, 2H), 5.17 (quint, J=7.0 Hz, 1H), 5.97 (bd, J=7.0 Hz, 1H), 6.31 (dt, J=15.8, 7.0 Hz, 1H), 6.52 (d, J=15.8 Hz, 1H), 7.24-7.39 (m, 10H). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.39; H, 7.41; N, 5.42.

*(E)-4-(4-Nitrophenyl)-N-(1-phenylethyl)-3-butenamide (E)-(**8f**).* M.p. 131-132°C (CCl_4); ^1H NMR ($CDCl_3$) δ 1.51 (d, J=7.0 Hz, 3H), 3.19 (d, J=5.5 Hz, 2H), 5.17 (quint, J=7.0 Hz, 1H), 5.89 (bd, J=7.0 Hz, 1H), 6.45-6.60 (m, 2H), 7.25-7.40 (m, 5H), 7.46 (d, J=8.8 Hz, 2H), 8.15 (d, J=8.8 Hz, 2H). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.89; H, 5.70; N, 9.28.

*(3E,5E)-6-Phenyl-N-(1-phenylethyl)-3,5-hexadienamide (E,E)-(**8g**).* M.p. 128-129°C (Et_2O/hexane); ^1H NMR ($CDCl_3$) δ 1.40 (d, J=7.0 Hz, 3H), 3.01 (d, J=7.5 Hz, 2H), 5.06 (quint, J=7.0 Hz, 1H), 5.81 (dt, J=15.1, 7.5 Hz, 1H), 5.90 (bd, J=7.0 Hz, 1H), 6.25 (dd, J=15.1, 10.6 Hz, 1H), 6.46 (d, J=15.2 Hz, 1H), 6.69 (dd, J=15.2, 10.6 Hz, 1H), 7.11-7.34 (m, 10H). Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.27; N, 4.81. Found: C, 82.31; H, 7.20; N, 4.63.

*4-Methyl-N-(1-phenylethyl)-3-pentenamide (**8h**).* Oil; ^1H NMR ($CDCl_3$) δ 1.39 (d, J=7.0 Hz, 3H), 1.62-1.79 (m, 6H), 2.83 (d, J=6.0 Hz, 1H), 5.18 (quint, J=7.0 Hz, 1H), 5.27 (tq, J=6.0, 1.0 Hz, 1H), 5.93 (bd, J=7.0 Hz, 1H), 7.13-7.33 (m, 5H). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.22; H, 8.61; N, 6.73.

*Ethyl 3-diethoxyphosphoryl-4-oxo-4-phenylbutanoate (**11**).*

A solution of diethyl 2-oxo-2-phenylethylphosphonate (**10**) (5.0g, 19.5 mmol) in THF (20 mL) was added dropwise to a stirred suspension of NaH (0.51 g, 21.4 mmol) in THF (30 mL) at 0°C. Stirring was continued for 1h at the same temperature and then ethyl bromoacetate (3.3 g, 19.5 mmol) in THF (15 mL) was added. Reaction mixture was stirred for additional 3h at 0°C and then warmed to room temperature. Water (30 mL) was added, the layers were separated, the aqueous layer was extracted with $CHCl_3$ (3x20 mL),and the combined organic extracts were dried and evaporated under reduced pressure to give the crude product. Vacuum distillation yielded pure **11** (4.4 g, 66%) as an oil. B.p. 153-156 °C/0.2 mmHg; ^1H NMR ($CDCl_3$) δ 0.97 (t, J=7.0 Hz, 6H), 1.09 (t, J=7.0 Hz, 3H), 2.73 (ddd, J=17.5, 9.0, 4.0 Hz, 1H), 3.30 (ddd, J=17.5, 10.5, 7.0 Hz, 1H), 3.65-4.09 (m, 6H), 4.43 (ddd, J=24.0, 10.5, 4.0 Hz, 1H), 7.15-7.48 (m, 3H), 7.73-8.01 (m, 2H); ^{31}P NMR ($CHCl_3$) δ 21.32. Anal. Calcd for $C_{16}H_{23}O_6P$: C, 56.14; H, 6.77; P, 9.05. Found: C, 56.01; H, 6.59; P, 9.15.

*Reduction of **11** with $NaBH_4$.*

The ketone **11** (1.0 g, 2.9 mmol) was dissolved in ethanol (30 mL) containing 12 drops of 10% aqueous NaOH. $NaBH_4$ (0.12 g, 3.2 mmol) was then added and the solution was stirred at room temperature for 20 h. After this time 5% aqueous HCl solution (15 mL) was added, ethanol was removed under reduced pressure and the aqueous layer was extracted with $CHCl_3$ (3x20 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ solution (2x20 mL), dried and evaporated under reduced pressure to give crude lactone **5c** as a 8:2 mixture of *cis* and *trans* isomers respectively. After purification and separation by column chromatography (silica gel, EtOAc/MeOH, 9.5:0.5, as eluent) pure *cis*-**5c** (0.60 g, 69%) and *trans*-**5c** (0.16 g, 17%) were obtained. Their spectral data were identical with the data described above.

(1R,2S*)-Diethyl 2-hydroxy-1-(2-hydroxyethyl)-3-methylbutylphosphonate (**13**).*

A mixture of *trans*-**5b** (1.0 g, 3.8 mmol), $LiBH_4$ (0.12 g, 5.7 mmol), and MeOH (0.18 g, 5.7 mmol) in Et_2O (15 mL) was refluxed for 20 minutes. The reaction was quenched with 1N aqueous HCl solution to pH ~ 1, water (4 mL) was added, and the mixture was extracted with CH_2Cl_2 (4x10 ml). The combined extracts were dried and solvent was evaporated under reduced pressure to give the crude product. Column chromatography (silica gel, EtOAc/MeOH, 9.5:0.5, as eluent) afforded pure **13** (0.79 g, 77%). Oil; ^{1}H NMR ($CDCl_3$) δ 0.78 (d, J=6.5 Hz, 3H), 0.94 (d, J=6.5 Hz, 3H), 1.25 (t, J=7,0 Hz, 3H), 1.26 (t, J=7.0 Hz, 3H), 1.70-1.85 (m, 1H), 1.89 (dq, J=23.0, 5.6 Hz, 2H), 2.17 (ddt, J=22.6, 2.3, 5.6 Hz, 1H), 3.56 (dt, J=2.3, 9.2 Hz, 1H), 3.64 (dt, J=11.5, 5.6 Hz, 1H), 3.72 (dt, J=11.5, 5.6 Hz, 1H), 3.80-4.30 (m, 6H); ^{31}P NMR ($CHCl_3$) δ 33.94. Anal. Calcd for $C_{11}H_{25}O_5P$: C, 49.24; H, 9.39; P, 11.54. Found: C, 49.21; H, 9.48; P, 11.67.

(1R,2S*)-Diethyl 2-hydroxy-3-methyl-1-[2-(triphenylmethoxy)ethyl]butylphosphonate (**14**).*

A solution of **13** (0.7 g, 2.61 mmol), tritylchloride (0.8 g, 2.88 mmol), triethylamine (0.5 mL) and 4-N,N-dimethylaminopyridine (30 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) was stirred for 12 h at room temperature. Then water (10 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (3x10 mL). The organic extracts were washed with saturated ammonium chloride solution (10 mL), water (10 mL), and dried. After removal of the solvent under reduced pressure the crude product was purified by column chromatography (silica gel, EtOAc/MeOH/Et_3N, 9.5:0.45:0.05, as eluent). Recrystallization from EtOAc/hexane gave pure **14** (0.87 g, 65%) as a white crystals. M.p. 130-131°C; ^{1}H NMR ($CDCl_3$) δ 0.81 (d, J=6.5 Hz, 3H), 1.02 (d, J=6.5 Hz, 3H), 1.17 (t, J=7.0 Hz, 3H), 1.24 (t, J=7.0 Hz, 3H), 1.81 (d heptet, J=9.0, 6.5 Hz, 1H), 1.89-2.15 (m, 2H), 2.21 (dddd, J=21.5, 8.0, 3.8, 1.3 Hz, 1H), 3.18 (dt, J=9.1, 6.7 Hz, 1H), 3.30 (dt, J=9.1, 6.2 Hz, 1H), 3.61 (ddd, J=11.3, 9.0, 1.3 Hz, 1H), 3.93-4.06 (m, 4H), 7.17-7.46 (m, 15H); ^{31}P NMR ($CHCl_3$) δ 34.67. Anal. Calcd for $C_{30}H_{39}O_5P$: C, 70.57; H, 7.70; P, 6.07. Found: C, 70.63; H, 7.75; P, 6.21.

*(E)-4-(5-Methyl-1-oxo-2-hexenyl)morpholine (**16**).*

A solution of **17** (1.0 g, 3.8 mmol) in THF (15 mL) was added at -70°C to a solution of LDA (4.6 mmol) in THF (10 mL) and the reaction mixture was stirred for 0.5 h maintaining this temperature. Then isovaleraldehyde (0.4 g, 4.6 mmol) was added at -70°C. The resulting mixture was stirred for 1 h at room temperature, water (20 mL) was added, and the aqueous layer was extracted with $CHCl_3$ (3x15 mL). The combined organic layers were dried and the solvent was evaporated. The crude product was purified by column chromatography (silica gel, EtOAc/MeOH, 9.5:0.5, as eluent) to give pure **16** (0.64 g; 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J=6.7 Hz, 6H), 1.72-1.81 (m, 1H), 2.11 (dt, J=1.5, 7.4 Hz, 2H), 3.57-3.74 (m, 8H), 6.20 (dt, J=15.1, 1.5 Hz, 1H), 6.89 (dt, J=15.1, 7.4 Hz, 1H). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.89; H, 9.51; N, 7.38.

*4-(2-Diethoxyphosphoryl-1-oxoethyl)morpholine (**17**).*

To a stirred solution of morpholine (2.6 g, 30 mmol) in Et_2O (40 mL) diethoxyphosphorylacetyl chloride (3.2 g, 15 mmol) was added at -20°C. The reaction mixture was warmed to room temperature and stirred for 0.5 h. Then water (30 mL) was added and the reaction mixture was extracted with $CHCl_3$ (3x30 mL). The combined organic layers were washed with 5% aqueous HCl solution (20 mL), saturated $NaHCO_3$ solution (20 mL) and saturated NaCl solution (20 mL), dried, and the solvent was evaporated to give the crude product. Distillation in vacuum yielded pure **17** (2.4 g; 60%) as a colorless oil. B.p. 100-102°C/1.5 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J=7.0 Hz, 6H), 3.17 (d, J=23.0 Hz, 2H), 3.60-3.97 (m, 8H), 4.02-4.62 (m, 4H); ^{31}P NMR ($CHCl_3$) δ 21.38. Anal Calcd for $C_{10}H_{20}NO_5P$: C, 45.28; H, 7.60; N, 5.28; P, 11.68. Found: C, 45.47; H, 7.53; N, 5.44; P, 4.39.

*Reaction of (E)- **8c** with t-BuOK/t-BuOH.*

A solution of (E)-**8c** (0.1 g) and t-BuOK (10mg) in t-BuOH (5 mL) was left at room temperature for 5 days. Then saturated NaCl solution (5 mL) was added and the reaction mixture was extracted with $CHCl_3$ (4x10 mL). Extracts were dried and evaporated to give yellow oil (90 mg). Integration of ^{1}H NMR spectrum showed the (E)-**8c**:**16** ratio to be 20:80. This ratio did not change when the above mixture was treated with t-BuOK/t-BuOH at room temperature for additional 3 days.

*Reaction of (E)-**8c** with morpholine.*

A solution of (E)-**8c** (0.1 g) and morpholine (0.5 g) in xylene (5 mL) were refluxed for 15 h. Then morpholine and xylene were evaporated in high vacuum to leave the yellow oil ($\sim$0.1 g). Integration of the ^{1}H NMR spectrum showed the (E)-**8c**:**16** ratio to be 95:5. Further reflux of the 95:5 mixture with morpholine (0.5 g) and xylene (5 mL) for 80 h gave mixture of (E)-**8c**:**16** in the ratio 75:25.

*Reaction of (E)-**8b** with 1-phenylethyl(D_2)amine.*

A solution of (E)-**8b**(0.1 g, 0.43 mmol) and 1-phenylethyl(D_2)amine (2.0 g, 8.6 mmol) in xylene (5mL)

was refluxed for 8 h. After cooling to room temperature the reaction mixture was washed with 5% aqueous HCl solution (2x10 mL), and washings were extracted with $CHCl_3$ (3x10 mL). The combined organic layers were dried and evaporated to give crude **18** as a slightly yellow oil. ^1H NMR ($CDCl_3$) δ 1.02 (d, J=6.8 Hz, 6H), 1.49 (d, J=7.0 Hz, 3H), 2.34 (octet, J=6.8 Hz, 1H), 2.94-3.00 (m, 0.2H), 5.13 (quint, J=7.0 Hz, 1H), 5.46-5.54 (m, 1H), 5.61 (dd, J=15.5, 6.8 Hz, 1H), 6.06-6.19 (bd, J=7.0 Hz, 1H), 7.24-7.43 (m, 5H).

*Diethoxyphosphoryl-N-(1-phenylethyl)acetamide (**19**).*

Phosphonate **19** was obtained according to the procedure described for **17** starting from diethoxyphosphorylacetyl chloride (3.2 g, 15 mmol) and 1-phenylethylamine (3.6 g, 30 mmol). Distillation of the crude product gave pure **19** (3.5 g, 78%). B.p. 87-90°C/0.1 mmHg; ^1H NMR ($CDCl_3$) δ 1.23 (t, J=7.0 Hz, 3H), 1.32 (t, J=7.0 Hz, 3H), 1.48 (d, J=7.0 Hz, 3H), 2.84 (d, J=20.6 Hz, 2H), 3.73-4.35 (m, 4H), 5.11 (quint, J=7.0 Hz, 1H), 7.10-7.48 (m, 6H); ^{31}P NMR ($CHCl_3$) δ 23.09. Anal. Calcd for $C_{14}H_{22}NO_4P$: C, 56.18; H, 7.41; N, 4.68; P, 10.35. Found: C, 56.34; H, 7.62; N, 4.48; P, 10.13.

*(E)-4-Phenyl-N-(1-phenylethyl)-2-butenamide (**20**).*

This compound was obtained according to the procedure described for **16** starting from **19** (1.0 g, 3.3 mmol) and phenylacetaldehyde (0.43 g, 3.6 mmol). Recrystallization of the crude product from AcOEt/Et_2O gave pure **20** (0.67 g, 76%) as a white crystals. M.p. 133-134°C; ^1H NMR ($CDCl_3$) δ 1.47 (d, J=7.5 Hz, 3H), 3.46 (dd, J=6.3, 1.5 Hz, 2H), 5.17 (quint, J=7.5 Hz, 1H), 5.70 (dt, J=15.8, 1.5 Hz, 1H), 6.95 (dt, J=15.8, 6.3 Hz, 1H), 7.12-7.41 (m, 11H). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.22; H, 7.15; N, 5.43.

*Reaction of **20** with 1-phenylethylamine.*

A solution of amide **20** (0.1 g) and 1-phenylethylamine (0.5 g) in xylene (5 mL) was refluxed for 8 h. Then 1-phenylethylamine and xylene were evaporated in high vacuum to leave the yellow oil. ^1H NMR spectrum showed product to be the mixture of **20** and (E)-**8e** in 5:95 ratio respectively.

*Preparation of the lactones **22a-d**. General procedure.*

To a solution of LDA (4.2 mmol) in THF (10 mL) was added a solution of the lactone *trans*-**5b** (1.0 g, 3.8 mmol) in THF (10 mL) at -70°C. The reaction mixture was stirred for 0.5 h at this temperature, and alkyl- or allyl-halide **21** (5.7 mmol) in THF (5mL) was then added. Stirring was continued for additional 2 h at room temperature. Addition of water (10 mL), extraction with Et_2O (3x15 mL) and removal of the solvent in vacuo gave crude lactones **22a-d** which were purified by column chromatography (silica gel, EtOAc/MeOH, 9.5:0.5, as eluent).

4-Diethoxyphosphoryl-4,5-dihydro-5-isopropyl-3-methyl-2(3H)-furanone (22a). Oil; ^{1}H NMR[15] ($CDCl_3$) *r-3,t-4,c-5-***22a** δ 0.86 (d, J=6.7 Hz, 3H), 1.01 (d, J=6.7 Hz, 3H), 1.28 (t, J=7.0 Hz, 6H), 1.29 (d, J=7.0 Hz, 3H), 1.88-2.07 (m, 1H), 2.14 (ddd, J=15.7, 10.2, 8.9 Hz, 1H), 2.83 (dddq, J=19.3, 10.2, 1.0, 7.0 Hz, 1H), 4.02-4.19 (m, 4H), 4.37(dddd, J=13.3, 8.9, 3.2, 1.0 Hz, 1H); *r-3,c-4,t-5-***22a** δ 0.95 (d, J=6.7 Hz, 3H), 1.07 (d, J=6.7 Hz, 3H), 1.28-1.35 (m, 9H), 1.88-2.07 (m, 1H), 2.25 (dddq, J=7.4, 1.7, 1.0, 7.0 Hz, 1H), 2.52 (ddd, J=19.1, 9.0, 7.4 Hz, 1H), 4.02-4.19 (m, 4H), 4.44 (dddd, J=10.7, 9.0, 2.2, 1.0 Hz, 1H); ^{31}P NMR[15] ($CHCl_3$) *r-3,t-4,c-5-***22a** δ 25.93; *r-3,c-4,t-5-***22a** δ 23.30. Anal. Calcd for $C_{12}H_{23}O_5P$: C, 51.79; H, 8.33; P, 11.13. Found: C, 51.71; H, 8.20; P, 11.45.

t-4-Diethoxyphosphoryl-r-3-ethyl-4,5-dihydro-c-5-isopropyl-2-(3H)-furanone (22b). Oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J=6.5 Hz, 3H), 0.99 (t, J=6.5 Hz, 3H), 1.10 (d, J=6.5 Hz, 3H), 1.34 (t, J=7.0 Hz, 6H), 1.79 (quint, J=6.5 Hz, 2H), 1.87-2.05 (m, 1H), 2.22 (ddd, J=16.0, 10.5, 8.5 Hz, 1H), 2.73-2.89 (m, 1H), 4.00-4.22 (m, 4H), 4.49 (ddd, J=12.8, 8.5, 3.9 Hz, 1H); ^{31}P NMR ($CHCl_3$) δ 24.22. Anal. Calcd for $C_{13}H_{25}O_5P$: C, 53.41; H, 8.62; P, 10.60. Found: C, 53.59; H, 8.48; P, 10.37.

r-3-Allyl-t-4-diethoxyphosphoryl-4,5-dihydro-c-5-isopropyl-2-(3H)-furanone (22c). Oil; ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J=6.5 Hz, 3H), 1.01 (d, J=6.5 Hz, 3H), 1.30 (t, J=7.0 Hz, 6H), 1.91 (d heptet, J=3.8, 6.5 Hz, 1H), 2.36-2.51 (m, 2H), 2.54-2.67 (m, 1H), 3.00 (ddt, J=20.2, 10.0, 4.9 Hz, 1H), 4.04-4.18 (m, 4H), 4.37 (ddd, J=14.1, 8.5, 3.8 Hz, 1H), 5.08-5.19 (m, 2H), 5.67 (dddd, J=15.9, 10.8, 8.3, 6.1 Hz, 1H); ^{31}P NMR ($CHCl_3$) δ 25.93. Anal. Calcd for $C_{14}H_{25}O_5P$: C, 55.25; H, 8.28; P, 10.18. Found: C, 55.09; H, 8.33; P, 10.34.

r-3-(2-Bromoallyl)-t-4-diethoxyphosphoryl-4,5-dihydro-c-5-isopropyl-2(3H)-furanone (22d). Oil; ^{1}H NMR ($CDCl_3$) δ 0.99 (d, J=6.7 Hz, 3H), 1.09 (d, J=6.7 Hz, 3H), 1.35 (t, J=7.0 Hz, 3H), 1.36 (t, J=7.0 Hz, 3H), 1.99 (d heptet, J=4.3, 6.7 Hz, 1H), 2.55 (ddd, J=16.9, 9.3, 8.0 Hz, 1H), 2.94 (d, J=6.0 Hz, 2H), 3.19 (ddt, J=20.6, 9.3, 6.0 Hz, 1H), 4.11-4.25 (m, 4H), 4.46 (ddd, J=14.6, 8.0, 4.3 Hz, 1H), 5.60 (d, J=1.8 Hz, 1H), 5.78 (d, J=1.8 Hz, 1H); ^{31}P NMR ($CHCl_3$) δ 25.58. Anal Calcd for $C_{14}H_{24}BrO_5P$: C, 43.88; H, 6.31; Br, 20.85; P, 8.08. Found: C, 43.76; H, 6.45; Br, 20.51; P, 8.13.

Preparation of the amides ***24a-d****. General procedure.*

Amides **24a-d** were prepared according to the procedure described for amides **8a-h**. Reaction time is given in the Table 3. Crude products were purified by column chromatography (silica gel, EtOAc/MeOH, 9.5:0.5, as eluent).

(E)-2,5-Dimethyl-N-(1-phenylethyl)-3-hexenamide (24a). Oil; ^{1}H NMR[16] ($CDCl_3$) δ 0.96 (d, J=6.5 Hz, 3H), 0.97 (d, J=6.5 Hz, 3H), 0.99 (d, J=6.5 Hz, 6H), 1.23 (d, J=7.0 Hz, 3H+3H), 1.44

(d, J=7.0 Hz, 3H), 1.45 (d, J=7.0 Hz, 3H), 2.21-2.37 (m, 1H+1H), 2.85-2.99 (m, 1H+1H), 5.09 (quint, J=7.0 Hz, 1H+1H), 5.43 (ddd, J=15.5, 6.7, 1.2 Hz, 1H), 5.47 (ddd, J=15.5, 6.7, 1.2 Hz, 1H), 5.55 (ddd, J=15.5, 7.7, 1.2 Hz, 1H), 5.56 (ddd, J=15.5, 7.7, 1.2 Hz, 1H), 6.06-6.16 (bd, J=7.0 Hz, 1H+1H), 7.20-7.37 (m, 5H+5H). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.44; H, 9.32; N, 5.97.

*(E)-2-Ethyl-5-methyl-N-(1-phenylethyl)-3-hexenamide (**24b**).* Oil; ^{1}H NMR[16] ($CDCl_3$) δ 0.95-1.10 (m, 9H+9H), 1.29-1.40 (m, 2H+2H), 1.45 (d, J=7.0 Hz, 3H), 1.46 (d, J=7.0 Hz, 3H), 2.23-2.40 (m, 1H+1H), 2.88-3.04 (m, 1H+1H), 5.05 (quint, J=7.0 Hz, 1H+1H), 5.49 (ddd, J=15.7, 6.5, 1.0 Hz, 1H), 5.55 (ddd, J=15.7, 6.5, 1.0 Hz, 1H), 5.65 (ddd, J=15.7, 7.5, 1.0 Hz, 1H), 5.67 (ddd, J=15.7, 7.5, 1.0 Hz, 1H), 6.31 (db, J=7.0 Hz, 1H+1H), 7.21-7.40 (m, 5H+5H). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.71; H, 9.72; N, 5.44. Found: C, 78.56; H, 9.84; N, 5.69.

*(E)-2-Allyl-5-methyl-N-(1-phenylethyl)-3-hexenamide (**24c**).* Oil; ^{1}H NMR[16] ($CDCl_3$) δ 0.96 (d, J=6.8 Hz, 3H), 0.97 (d, J=6.8 Hz, 3H), 0.99 (d, J=6.8 Hz, 6H), 1.45 (d, J=7.0 Hz, 3H), 1.46 (d, J=7.0 Hz, 3H), 2.21-2.36 (m, 2H+2H), 2.54 (d octet, J=1.1, 6.8 Hz, 1H), 2.55 (d octet, J=1.1, 6.8 Hz, 1H), 2.81 (q, J=8.0 Hz, 1H), 2.83 (q, J=8.0 Hz, 1H), 4.96-5.09 (m, 2H+2H), 5.10 (quint, J=7.0 Hz, 1H+1H), 5.38 (ddd, J=15.0, 8.0, 1.1 Hz, 1H), 5.42 (ddd, J=15.0, 8.0, 1.1 Hz, 1H), 5.53 (dd, J=15.0, 6.8 Hz, 1H), 5.54 (dd, J=15.0, 6.8 Hz, 1H), 5.71 (ddt, J=16.7, 10.1, 7.0 Hz, 1H), 5.74 (ddt, J=16.7, 10.1, 7.0 Hz, 1H), 5.93 (bd, J=7.0 Hz, 1H+1H), 7.22-7.37 (m, 5H+5H). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.41; H, 9.53; N, 5.02.

*(E)-2-(2-Bromoallyl)-5-methyl-N-(1-phenylethyl)-3-hexenamide (**24d**).* Oil; ^{1}H NMR[16] ($CDCl_3$) δ 1.04 (d, J=6.5 Hz, 3H), 1.05 (d, J=6.5 Hz, 3H), 1.10 (d, J=6.5 Hz, 6H), 1.48 (d, J=7.0 Hz, 3H), 1.49 (d, J=7.0 Hz, 3H), 2.57 (d octet, J=1.0, 6.5 Hz, 1H), 2.58 (d octet, J=1.0, 6.5 Hz, 1H), 2.78-3.01 (m, 3H+3H), 5.13 (quint, J=7.0 Hz, 1H+1H), 5.39-5.63 (m, 2H+2H), 5.63 (d, J=1.8 Hz, 1H), 5.64 (d, J=1.8 Hz, 1H), 5.80 (d, J=1.8 Hz, 1H), 5.81 (d, J=1.8 Hz, 1H), 6.05 (bd, J=7.0 Hz, 1H+1H), 7.28-7.45 (m, 5H+5H). Anal. Calcd for $C_{18}H_{24}BrNO$: C, 61.71; H, 6.91; N, 4.00. Found: C, 61.55; H, 6.79; N, 4.15.

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15. Values for specific isomer were taken from the spectrum of the mixture of isomers.

16. Values for both diastereoisomers taken from the spectrum of the 1:1 mixture of isomers.

(*Received in UK* 7 *November* 1994; *accepted* 25 *November* 1994)