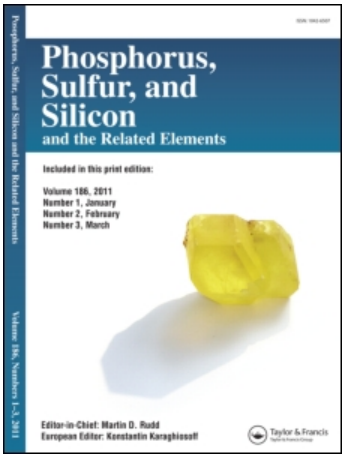

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SYNTHESIS OF PHOSPHONIC ACIDS RELATED TO THE ANTIBIOTIC FOSMIDOMYCIN FROM ALLYLIC α- AND γ-HYDROXYPHOSPHONATES†

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Pd(0) catalyzed amination of dialkyl (1-methoxycarbonyloxy-2-alkenyl)phosphonates **4** (R^3 = H) with the N,O-alkoxycarbonyl protected hydroxylamines BocNHOBoc (**3a**) and MocNHOMoc (**3b**) proceeds regiospecifically and with high (*E*)-stereoselectivity to give the protected (3-N-hydroxyamino-1-alkenyl)-phosphonates **5** and **6**, respectively, with very good yields. Alternatively compounds **5** and **6** are obtained in excellent yields from the (3-hydroxy-1-alkenyl)phosphonates **2** under Mitsunobu conditions using **3a** and **3b**, respectively, as nucleophiles. Much less satisfactory yields of compounds **7** and **8** have been obtained in both pathways using the hydroxylamine derivatives BocNHOBn (**3c**), and AcNHOAc (**3d**), respectively, as nucleophiles. Compounds **5–8** have been further transformed to various precursors and analogues of the natural phosphonic acid antibiotics FR 32863 and FR 31564 (fosmidomycin).

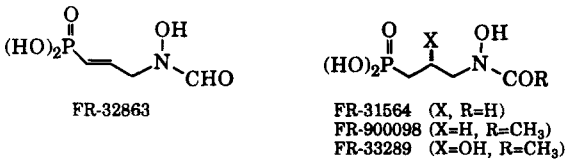
Key words: (3-N-hydroxyamino-1-alkenyl)phosphonic acids, phosphonate substituted allylic carbonates, N-hydroxyamination, N-hydroxyureas, *tert*-butyl (*tert*-butoxycarbonyloxy)carbamate, rotational restriction.

INTRODUCTION

In 1980, the Fujisawa Company reported the isolation of four related phosphonic acid antibiotics from the culture broth of *Streptomyces* strains.[1–6] The compounds contain a unique hydroxamic acid functionality in the γ-position of a prop(en)yl skeleton (Scheme I), and exhibit high antibacterial activity. The most active compound (FR 31564, fosmidomycin), which is now assumed to act by inhibition of the bacterial isoprenoid synthesis,[7] has been the object of extensive pharmacological studies, and was recommended for further clinical evaluation.[8] Since the discovery of these natural compounds extensive synthetic activity revealed interesting antibiotic, bactericidal and herbicidal properties of synthetic N-hydroxyaminophosphonic acid derivatives.[9–12]

In continuation of our work dealing with the synthetic potential of allylic hydroxyphosphonates[13] we present here two very efficient routes to variously substituted [3-N-hydroxyamino-1-alk(en)yl]phosphonic acid derivatives through N-hydroxyamination of allylic α- or γ-hydroxyphosphonates.

†Presented in part at the XIIIth ICPC, Jerusalem, Israel, July 16–21, 1995.



FR-32863

FR-31564 (X, R=H)
FR-900098 (X=H, R=CH_3)
FR-33289 (X=OH, R=CH_3)

SCHEME I

REGIOSELECTIVE PALLADIUM(0) CATALYZED AMINATION OF CARBONATES OF ALLYLIC α-HYDROXYPHOSPHONATES WITH HYDROXYLAMINE DERIVATIVES

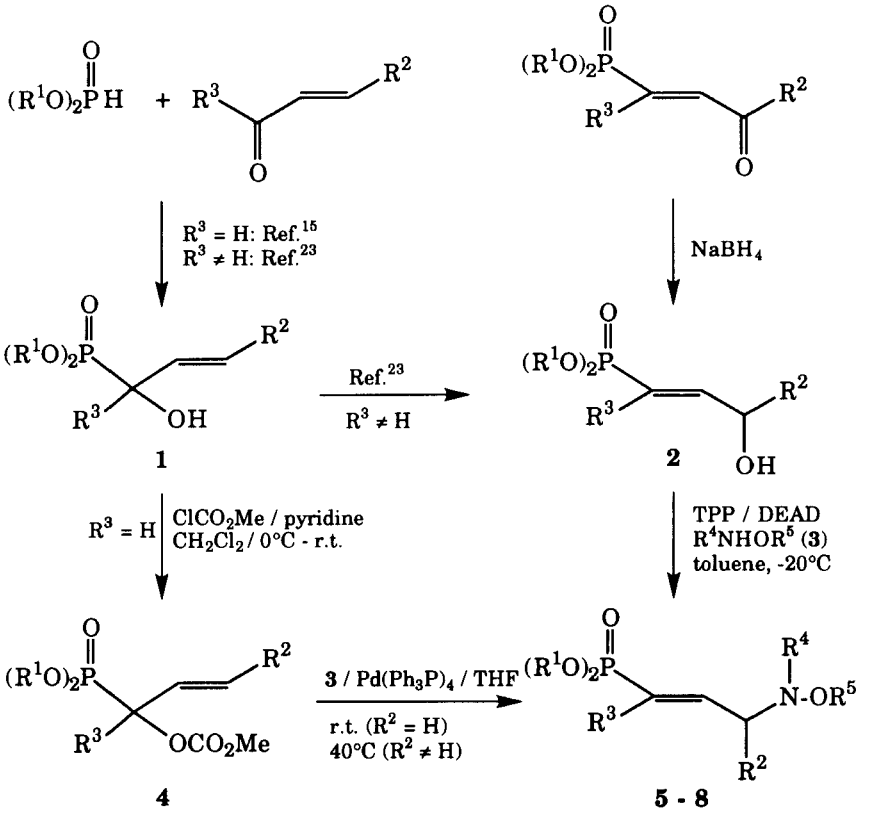
As part of a study of the utility of allylic α-hydroxyphosphonates for the 1,3-interchange of functionality we recently developed a novel and convenient route to the natural antibiotics FR 32863, FR 31564, and FR 900098 (Scheme I), the key step being the regioselective amination of the acrolein derived allylic carbonate **4b** (R^3, R^2 = H) with *tert*-butyl (*tert*-butoxycarbonyloxy)carbamate (BocNHOBoc, **3a**).[14]

This part of our report describes the results of an application of this method to homologous aldehyde derived carbonates **4** (R^3 = H, $R^2 \neq$ H) in the reaction with BocNHOBoc (**3a**), as well as with the hydroxylamine derivatives MocNHOMoc (**3b**), BocNHOBn (**3c**), and AcNHOAc (**3d**). The starting α-hydroxyphosphonates **1** are easily available by the regioselective, fluoride catalyzed 1,2-addition of dialkyl phosphites to α,β-unsaturated aldehydes,[15] and are further converted to the carbonates **4** under standard conditions. Addition of dialkylphosphites and subsequent acylation with methyl chloroformate can also be effected by a "one pot procedure" as exemplified in the Experimental Part.

The Pd(0) catalyzed amination of compounds **4a–e** with BocNHOBoc (**3a**) proceeded smoothly to yield the 3-substituted (1-alkenyl)phosphonates **5** with complete regiocontrol and with high (*E*)-stereoselectivity (Table I, entries 1–5). Use of the *bis*-methoxycarbonyl substituted analogue (MocNHOMoc, **3b**) provided satisfactory results with propenylphosphonates (entry 6), as well as with the crotonaldehydede derived carbonate **4d** (entry 7), but we have not been able to isolate the 3-phenyl-substituted derivative **6e** from the complex reaction mixture obtained upon reacting carbonate **4e** with **3b** (run 8). Using *t*-butyl N-benzyloxycarbamate (**3c**) as nucleophile, which could enable a selective removal of the protective groups, yield and stereocontrol were evidently less satisfactory, even with the most reactive propenylphosphonate **4a** (entry 9). Finally, the use of (N-acetyloxy)acetamide (AcNHOAc, **3d**), which previously has been used by us for the synthesis of (*E*)-**8b** (entry 10),[14] provided only a modest yield of the homologous butenylphosphonate (*E*)-**8c**, along with a substantial quantity of the corresponding (*E*)-1,3-butadienylphosphonate (entry 11).

ALKYLATION OF HYDROXYLAMINE DERIVATIVES WITH ALLYLIC γ-HYDROXYPHOSPHONATES BY MITSUNOBU REACTION

For the synthesis of α-substituted or cyclic compounds **5–8** with $R^3 \neq$ H we had to develop an alternative pathway. Stimulated by previous work of other authors,[16] we



1, 2, 4, 5-8, 10-13	a	b	c	d	e	f	g	h	i
R^1	Me	iPr	Me	iPr	iPr	Et	Me	Me	Me
R^2	H	H	Me	Me	Ph	Et	$(CH_2)_2$	$(CH_2)_3$	$(CH_2)_4$
R^3	H	H	H	H	H	Me			

	3a,5	3b,6	3c,7	3d,8
R^4	Boc	Moc	Boc	Ac
R^5	Boc	Moc	Bn	Ac

SCHEME II

investigated the direct N-alkylation of (3-hydroxy-1-alkenyl)phosphonates **2** with the hydroxylamine derivatives **3** under Mitsunobu's conditions.[20]

As outlined in Scheme II, the starting phosphonates **2** are easily available by methods elaborated in this laboratory: Open chain compounds **2** are obtained quantitatively by the reduction of the corresponding (3-oxo-1-alkenyl)phosphonates. The latter can be prepared either by Arbusov reaction of β-chlorovinylketones with trialkyl phosphites[21] (compounds with R^3 = H), or by Wittig olefination of acylphos-

TABLE I

Pd(0) catalyzed hydroxyamination of carbonates **4** with hydroxylamine derivatives **3**

Entry	4	3	Reaction Time (h)	Temp. (°C)	Product(s) (Yield, %)[a]	
1	**4a**	**3a**	2	r.t.	*E*-**5a** (85)	*Z*-**5a** (12)
2[b]	**4b**	**3a**	1.5	r.t.	*E*-**5b** (87)	*Z*-**5b** (5)
3[c]	**4c**	**3a**	3	40	*E*-**5c** (86)	*Z*-**5c** (2)
4	**4d**	**3a**	3.5	40	*E*-**5d** (70)	- -
5	**4e**	**3a**	2.5	40	*E*-**5e** (89)	-
6	**4b**	**3b**	1.5	r.t.	*E*-**6b** (90)	*Z*-**6b** (7)
7[d]	**4d**	**3b**	3.5	40	*E*-**6d** (75)	-
8[e]	**4e**	**3b**	4.5	40	-	-
9	**4a**	**3c**	1.5	r.t.	*E*-**7a** (49)	*Z*-**7a** (15)
10[b]	**4b**	**3d**	1.5	r.t.	*E*-**8b** (64)	*Z*-**8b** (10)
11[f]	**4c**	**3d**	1.5	40	*E*-**8c** (58)	-

[a]Yields of isolated compounds.

[b]Results taken from our preliminary communication in Reference 14.

[c]Dimethyl (*E*)-(3-methoxy-1-butenyl)phosphonate has been obtained as byproduct in ca. 5% yield.

[d]Diisopropyl (*E*)-1,3-butadienyl-phosphonate (11%) has been obtained as byproduct.

[e]**4e** was consumed, but **6e** could not be separated from the complex reaction mixture.

[f]Dimethyl (*E*)-1,3-butadienylphosphonate (18%) has been obtained as byproduct.

phonates $(R^1O)_2P(O)COR^3$ with 2-oxoalkylidene triphenylphosphoranes[22] $Ph_3P{=}CHCOR^2$ (compounds with $R^3 \neq H$). Cycloalkenyl derivatives as **2g–i** are most conveniently available by rearrangement of the corresponding 1-hydroxy isomers **1**.[23]

The TPP/DEAD mediated N-alkylation of the *bis*(alkoxycarbonyl)-substituted hydroxylamines **3a** and **3b** with various hydroxyphosphonates **2** proceeded smoothly in toluene at −20°C to give the corresponding protected N-hydroxyamino derivatives **5** and **6**, respectively, with excellent yields (Table II, entries, 1–7). However, the reaction of a 3-phenyl-substituted hydroxyphosphonate **2** (R^1 = *i*Pr, R^2 = Ph, R^3 = Me) with **3a** resulted in a complex reaction mixture, from which the corresponding amination product could not be isolated. Finally, reaction of **2d** with *t*-butyl (N-benzyloxy)carbamate (**3c**) provided only a very low yield of the corresponding phosphonate (*E*)-**7d**, together with a hydrazine derived substitution product, arising from the nucleophilic participation of diethyl hydrazo-1,2-dicarboxylate[24] (entry 8).

TABLE II

Hydroxyamination of γ-hydroxyphosphonates **2** with hydroxylamine derivatives **3a–c**[a] by Mitsunobu reaction

Entry	2	3	Reaction Time (h)	Product	Yield (%)[b]
1	**2d**	**3a**	1.5	*E*-**5d**	91
2	**2f**	**3a**	1	*E*-**5f**	95
3	**2g**	**3a**	1	**5g**	87
4	**2h**	**3a**	1.5	**5h**	95
5	**2i**	**3a**	4	**5i**	87
6	**2d**	**3b**	0.75	*E*-**6d**	91[c]
7	**2h**	**3b**	1	**6h**	89
8	**2d**	**3c**	2[d]	*E*-**7d**	28[e]

[a]AcNHOAc (**3d**) was not investigated in this pathway, as O-protected acetohydroxamates have been reported to react by predominant O-alkylation in intermolecular Mitsunobu reactions.[17]

[b]Yield of isolated compounds.

[c]Product contained 10–15% TPPO.

[d]1 h at −20°C, 1 h at r.t.

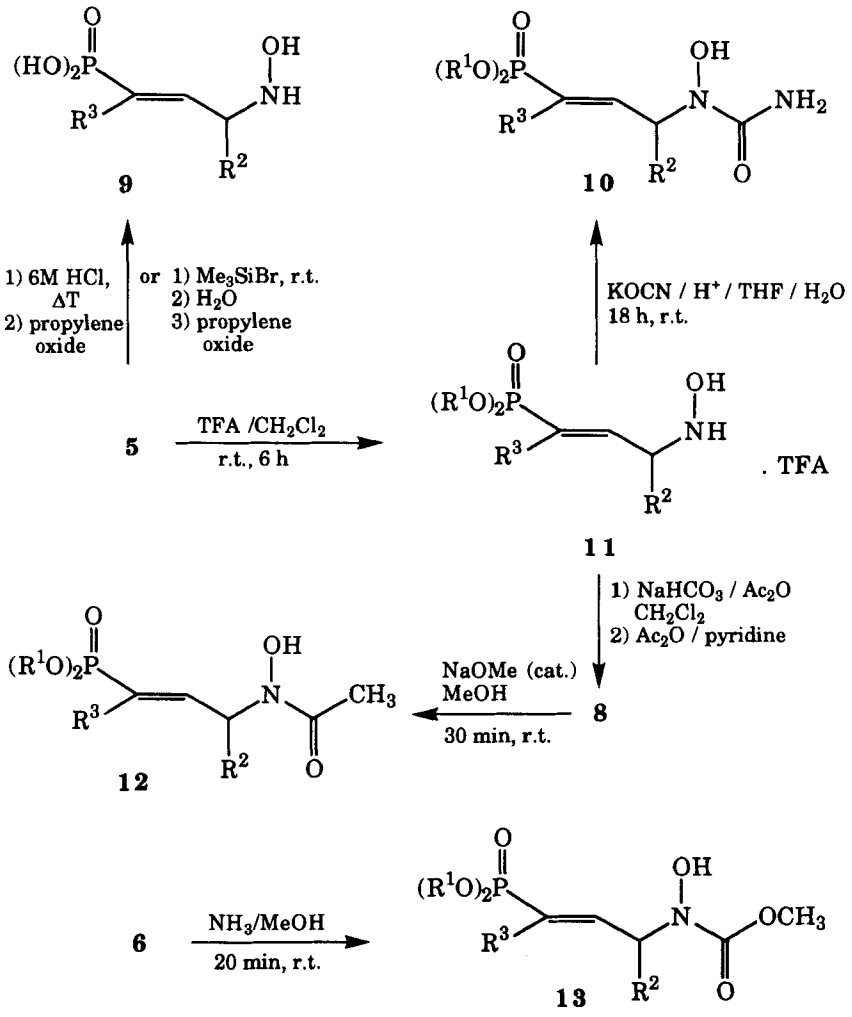
[e]A hydrazine derived γ-substitution product was isolated with 43% yield.

TRANSFORMATION OF COMPOUNDS 5–8

Some of the synthetic potential of compounds **5** (and **6**) has been demonstrated by the reactions outlined in Scheme III: Simultaneous removal of phosphonic acid and hydroxylamino protecting groups from compounds **5** (R^4, R^5 = Boc) was accomplished simply by refluxing in hydrochloric acid (6M), or by treatment with bromotrimethylsilane at room temperature, followed by hydrolysis to yield, upon subsequent treatment with propylene oxide, the new (3-hydroxy amino-1-alkenyl)-phosphonic acids **9**, precursors for homologues of the natural antibiotic FR 32863.

Selective removal of the Boc-groups from compounds **5** was effected with trifluoroacetic acid in dichloromethane at room temperature to give the trifluoroacetates **11**. These have been transformed to the N-hydroxy ureas **10**[26] by reaction with potassium cyanate in THF/H_2O, and to the diacetylated derivatives **8** by reaction with Ac_2O.[30] Selective cleavage of the O-acetyl bond in compounds **8** was achieved by sodium methoxide catalyzed transesterification in methanol to afford the hydroxamates **12**. Similarly, compounds **6** (R^4, R^5 = Moc) have been partially deprotected by brief treatment with NH_3/MeOH to give the N-hydroxy carbamates **13** with excellent yields.[31]

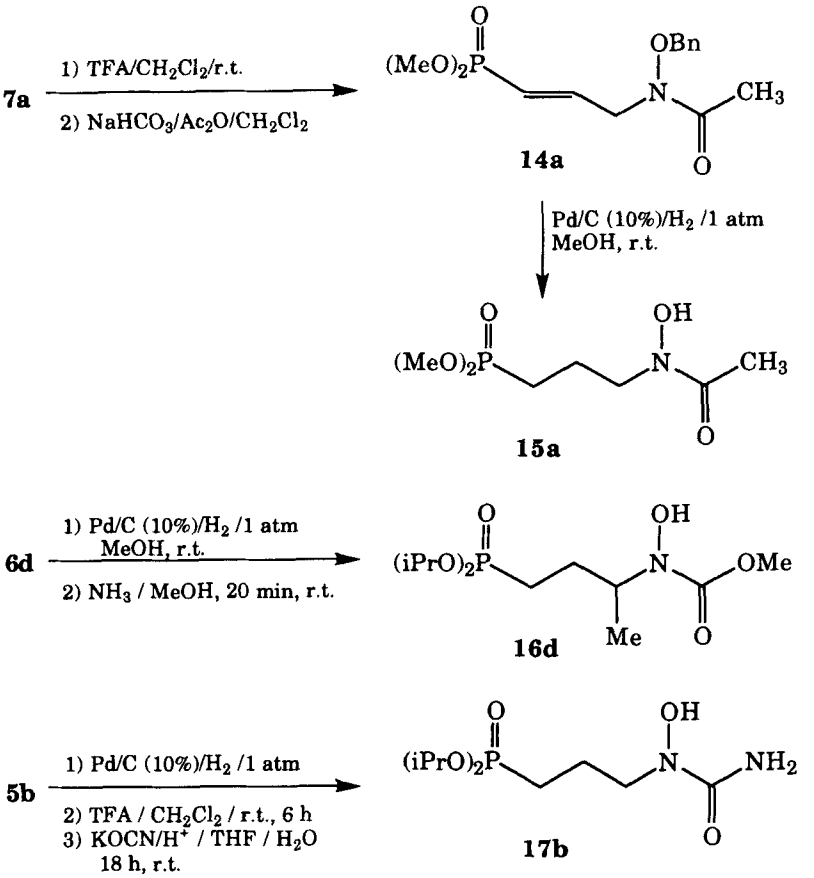
Finally, as outlined by the examples given in Scheme IV, hydrogenation over palladium-carbon of the unsaturated compounds **5–8** was shown to proceed without competitive cleavage of the N—O-bond to afford the corresponding saturated derivatives, which now bear the skeleton of the antibiotics fosmidomycin and FR 900098.



SCHEME III

SPECTROSCOPY OF N,O-DIACYLATED AND N-MONOACYLATED [3-N-HYDROXYAMINO-1-ALK(EN)YL]PHOSPHONATES

According to the literature data for N,O-diacylated hydroxylamines,[5,6,14,32,33] the infrared spectra of the fully protected phosphonates **5**, **6**, and **8** show two distinct carbonyl absorptions (Boc-protected compounds **5**: OCO at 1782–1793, NCO at 1705–1724 cm^{-1}; Moc-protected derivatives **6**: OCO at 1794–1799, NCO at 1732–1734 cm^{-1}; N,O-diacetylated compounds **8**: OCO at 1795–1798, NCO at 1676–1681 cm^{-1}). The carbonyl absorptions of the N-monoacylated compounds are shifted to 1633–1650 cm^{-1} (N-acetyl derivatives **12** and **15**), 1694–1706 (carbamates **13** and **16**), and 1644–1682 cm^{-1} (N-hydroxy ureas **10** and **17**), respectively.[14,32,33]



SCHEME IV

The CO-absorptions of O-acylhydroxylamines without an N-acyl substituent are reported to occur at ν = 1726–1745 cm^{-1}.[32,33] It should be mentioned, that the IR-spectrum of compound **15a**, depicted in Scheme IV (CO: ν = 1633 cm^{-1}) does not agree with the data reported for the compound produced by esterification of the natural antibiotic FR 900098 with diazomethane (two carbonyl absorptions at 1740 and 1640 cm^{-1}),[5] which suggest the presence of both types of monoacetylated compounds, in the latter case.

Satisfactory ^1H and ^{13}C-NMR spectra have been obtained at room temperature for all N-monoacylated compounds, and for most of the *bis*(methoxycarbonyl) protected derivatives **6**. However, very broad and unresolved signals have been observed in the ^1H-NMR spectra of all N,O-diacylated compounds **5** and **8** with $R^2 \neq H$, if measured in $CDCl_3$ at room temperature. Moreover, in the ^{13}C-NMR spectra of these compounds various signals (C-1 to C-3, CO) could not be detected at room temperature, evidently due to a rotational restriction of the N-acyl group.[34] Thus, for a complete analysis, most of these spectra had to be taken in toluene-d_8 at 90–100°C to give satisfactory results.

EXPERIMENTAL

Melting points were taken with a Kofler apparatus and are uncorrected. IR spectra (solids: Nujol, liquids: film on Si-plates[35] were recorded on a Perkin-Elmer FT 1650 Infrared spectrophotometer. ^1H and *J*-modulated ^{13}C NMR spectra were recorded on a Bruker WM 400 spectrometer. Mass spectra were obtained on a Finnigan MAT spectrometer 311A connected with a Vector 2/Teknivent data system. TLC was performed on Merck silica gel 60 F_{254} plates (visualization of alkenyl derivatives by $KMnO_4$/acetone spray, visualization of satd. compounds by iodine vapour). Flash chromatography was performed on glass columns packed with Merck silica gel 60 (230–400 mesh). THF was freshly distilled from potassium under Ar atmosphere prior to use. Oily dialkyl phosphonates were dried by repeated coevaporation with toluene prior to use. BocNHOBoc (**3a**) was prepared according to the new protocol given in Reference 36, MocNHOMoc (**3b**) was prepared by the procedure given in Reference 37, and was distilled over a 20 cm column at 0.01 Torr (b.p. 70–73°C) to give a colorless oil. BocNHOBn (**3c**) was prepared according to Reference 38, and AcNHOAc (**3d**) was prepared by the protocol given in Reference 39, and was stored at 4°C under Ar. The α-hydroxyphosphonates **1** with R^3 = H were prepared by the protocol of Texier-Boullet.[15] The (3-hydroxy-1-alkenyl)phosphonate **2d**[13a] was prepared by reduction of the corresponding (3-oxo-1-alkenyl)phosphonate with sodium borohydride. The cyclic analogues **2g**[23] and **2h**[23] have been prepared from 2-cyclopentenone and 2-cyclohexenone, respectively, by our protocol in Reference 40. **2i**[23] was prepared analogously from 2-cycloheptenone with 78% overall yield. Abbreviations: TPP = triphenylphosphane, TPPO = triphenylphosphane oxide, DEAD = diethyl 1,2-azodicarboxylate, TMSBr = bromotrimethylsilane, TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl, Moc = methoxycarbonyl, PE = petroleum ether.

Dialkyl (1-Methoxycarbonyloxy-2-alkenyl)phosphonates **4**

A. *From dialkyl (1-hydroxy-2-alkenyl)phosphonates* **1**. *General Procedure 1 (GP1)*: To a cold (0–5°C) stirred solution of dry **1** (10.0 mmol) and pyridine (1.90 g, 24.0 mmol) in dry dichloromethane (20 ml) is added dropwise under Ar a solution of methyl chloroformate (1.13 g, 12.0 mmol) in dichloromethane (20 ml). The ice bath is removed after 0.5 h, and stirring continued until disappearance of **1** (TLC control). Then the solution is extracted with 1 M HCl and brine (each 25 ml), dried (Na_2SO_4), and evaporated in vacuo. The residue is purified either by Kugelrohr distillation at 0.01 Torr or by flash chromatography on silica gel to yield **4** as a colorless oil.

B. *One pot procedure from α,β-unsaturated aldehydes. General Procedure 2 (GP2)*: A mixture of the α,β-unsaturated aldehyde (10.0 mmol), dialkylphosphite (10.0 mmol), and KF (2.90 g, 50 mmol) is stirred at r.t. under Ar until completion.[15] Then dry CH_2Cl_2 (35 ml) is added with vigorous stirring. The solids are rapidly filtered off and washed with dry CH_2Cl_2 (20 ml). The cooled (0–5°C) filtrate containing the crude α-hydroxyphosphonate **1** is further converted to **4** as given above.

Dimethyl (1-methoxycarbonyloxy-2-propenyl)phosphonate (**4a**): Acrolein (1.26 g, 22.4 mmol) and dimethyl phosphite (2.20 g, 20 mmol) were caused to react by *GP2*. Purification by Kugelrohr distillation (bath temp. 100–110°C/0.01 Torr), yield 3.31 g (74%).

Dimethyl (E)-(1-Methoxycarbonyloxy-2-butenyl)phosphonate (**4c**)

A. (*E*)-2-Butenal (2.25 g, 32 mmol) and dimethyl phosphite (3.30 g, 30 mmol) were caused to react according to *GP2*. Yield 4.50 g (63%) after Kugelrohr distillation (bath temp. 100–105°C/0.01 Torr).

B. **1c**[15] (5.40 g, 30 mmol) was caused to react according to *GP1*. Yield 6.43 g (90%).

Diisopropyl (E)-(1-Methoxycarbonyloxy-2-butenyl)phosphonate (**4d**)

1. *Diisopropyl (E)-(1-hydroxy-2-butenyl)phosphonate* (**1d**) was prepared with 85% yield by the KF catalyzed addition of diisopropyl phosphite to (*E*)-2-butenal analogously to the procedure of Texier-Boullet[15] (reaction time 24 h, TLC and flash chromatography with CH_2Cl_2/EtOAc, 1:1, R_f = 0.26, colorless crystals, m.p. 28°C).—^1H-NMR ($CDCl_3$): δ = 1.28 (d, 3H), 1.29 (br d, 6H), 1.30 (d, 3H) [*J* ≈ 6.4 Hz, POCH(C<u>H</u>$_3$)$_2$], 1.72 (m_c, 3H, C<u>H</u>$_3$CH), 3.30 (br s, 1H, OH), 4.29 (m_c, 1H, C<u>H</u>OH), 4.70 (m_c, 2H, POCH), 5.52–5.61, 5.77–5.88 (2m, each 1H, 2-H, 3-H).

2. **4d** *from* **1d** *by GP1*: colorless oil (Kugelrohr distillation, bath temp. 100–110°C/0.01 Torr, yield 93%, TLC: CH_2Cl_2/EtOAc, 7:3, **1d**: R_f = 0.22, **4d**: R_f = 0.66).

Diisopropyl (E)-(1-Methoxycarbonyloxy-3-phenyl-2-propenyl)phosphonate (**4e**):

1. *Diisopropyl (1-hydroxy-3-phenyl-2-propenyl)phosphonate* (**1e**) was prepared analogously to the procedure of Texier-Boullet[15] [reaction time 18 h, TLC: CH_2Cl_2/EtOAc, 1:1, R_f = 0.32, m.p. 88–90°C

TABLE III

Carbonates **4** prepared

	Procedure	Yield (%)	Molecular Formula	Elemental Analysis calc. (found) %C	%H	IR (Si) ν (cm^{-1})
4a	GP2	74	$C_7H_{13}O_6P$ (224.2)	37.50 (37.28)	5.86 (5.65)	1755, 1257, 1028
4c	GP2 GP1	63 90	$C_8H_{15}O_6P$ (238.2)	40.33 (40.51)	6.36 (6.18)	1751, 1255, 1027
4d	GP1	93	$C_{12}H_{23}O_6P$ (294.3)	48.97 (48.72)	7.89 (7.98)	1756, 1264, 991
4e	GP1	83	$C_{17}H_{25}O_6P$ (356.4)	57.29 (57.34)	7.08 (7.34)	1755, 1260, 991

TABLE IV

NMR data of carbonates **4** [$CDCl_3$, δ, J (Hz)]

	^{1}H-NMR	^{13}C-NMR
4a	3.80 (CO_2CH_3), 5.37 (m_c, 3-H_b), 5.44-5.52 (m, 2H,3-H_a, 1-H), 5.92 (dddd, $J_{2,a}$ = 17.2, $J_{2,b}$ = 10.8, $J_{2,1}$ = 5.9, $J_{2,P}$ = 4.4, 2-H).	55.35 (s, $CO_2\underline{C}H_3$), 72.82 ($^1J_{PC}$ = 168.5, PC), 119.69 ($^3J_{PC}$ = 11.5 Hz, C-3), 128.70 ($^2J_{PC}$ = 4.2, C-2), 154.60 ($^3J_{PC}$ = 9.3, CO)
4c	1.73 (m_c, $C\underline{H}_3CH$), 3.77 (s, CO_2CH_3), 5.39 (br dd, $J_{1,3} \approx 1$, $J_{1,2}$ = 7.9, $J_{1,P}$ = 12.8, 1-H), 5.54, 5.94 (2m_c, 2-H, 3-H)	17.92 ($\underline{C}H_3CH$), 55.20 ($CO_2\underline{C}H_3$), 72.89 ($^1J_{PC}$ = 171.5, PC), 121.48 ($^2J_{PC}$ = 3.8, C-2), 138.88 ($^3J_{PC}$ = 12.8, C-3), 154.68 ($^3J_{PC}$ = 10.0, CO)
4d	1.76 (m_c, $C\underline{H}_3CH$), 3.80 (s, CO_2CH_3), 5.34 (dd, $J_{1,2}$ = 7.9, $J_{1,P}$ = 12.8, 1-H), 5.57, 5.94 (2m_c, 2-H, 3-H)	17.84 ($\underline{C}H_3CH$), 55.00 ($CO_2\underline{C}H_3$), 73.69 ($^1J_{PC}$ = 173.6, PC), 122.07 ($^2J_{PC}$ = 3.7, C-2), 133.07 ($^3J_{PC}$= 12.6, C-3),154.84 ($^3J_{PC}$ = 10.4, CO)
4e	3.79 (s, CO_2CH_3), 5.55 (ddd, $J_{1,3} \approx 1$, $J_{1,2}$ = 7.4, $J_{1,P}$ = 14.3, 1-H), 6.22 (ddd, $J_{2,P}$ = 5.4, $J_{2,1}$ = 7.4, $J_{2,3}$ = 15.8, 2-H), 6.73 (br dd, $J_{3,1} \approx 1$, $J_{3,P}$ = 3.4, $J_{3,2}$ = 15.8, 3-H), 7.21-7.32 ($3H_{arom}$), 7.34-7.39 ($2H_{arom}$)	55.23 ($CO_2\underline{C}H_3$), 73.81 ($^1J_{PC}$ = 172.6, PC), 120.11 ($^2J_{PC}$ =4.3, C-2), 126.74 (J = 1.2, *o*-CH), 128.30 (*p*-CH), 128.56 (*m*-CH), 135.05 ($^3J_{PC}$ = 12.4, C-3), 135.73 (J_{PC} = 2.2, *i*-C), 154.87 ($^3J_{PC}$ = 10.1, CO)

(Et_2O)].—^{1}H-NMR ($CDCl_3$): δ = 1.32 (d, J = 6.4 Hz, 3H), 1.33 (d, J = 5.9 Hz, 6H), 1.34 (d, J = 5.9 Hz, 3H) [POCH($C\underline{H}_3$)$_2$], 4.07 (br s, 1H, OH), 4.61 (br dd, $J_{1,P}$ = 12.3, $J_{1,2}$ = 5.4 Hz, 1H, PCH), 4.77 (m_c, 2H, POCH), 6.31 (dt, $J_{2,3}$ = 15.8, $J_{2,1}$ = $J_{2,P}$ = 5.4 Hz, 1H, 2-H), 6.77 (ddd, $J_{3,2}$ = 15.8, $J_{3,P}$ = 4.9, $J_{3,1} \approx$ 1.5 Hz, 1H, 3-H), 7.24 (m, 1H), 7.31 (m, 2H), 7.39 (m, 2H).—^{13}C-NMR ($CDCl_3$): δ = 23.88, 23.96, 24.10, 24.14 [4d, J = 5.3, 4.8, 5.2, 4.9 Hz, POCH($\underline{C}H_3$)$_2$], 69.75 ($^1J_{PC}$ = 161.8 Hz, PC), 71.61 (J_{PC} = 7.5 Hz), 71.81 (J_{PC} = 7.4 Hz) [POCH], 124.26 (J_{PC} = 4.6 Hz, C-3), 126.55 (J_{PC} = 1.8 Hz, *o*-CH), 127.70 (*p*-CH), 128.51 (*m*-CH), 132.01 (J_{PC} = 13.0 Hz, C-2), 136.60 (J_{PC} = 2.9 Hz, *i*-C).

2. **4e** *from* **1e** *by GP1*: Yield 83%, TLC and flash chromatography: CH_2Cl_2/EtOAc, 19:1, R_f = 0.25.

Dialkyl N,O-Protected (3-N-Hydroxyamino-1-alkenyl)phosphonates **5–8**

A. *From allylic carbonates* **4**. *General Procedure 3 (GP3)*: To a solution of dry **4** and **3** (each 5.0 mmol) in dry THF (25 ml) is added $Pd(Ph_3P)_4$ (280 mg, 5 mol%) under Ar atmosphere. The solution is stirred at r.t. (propenyl compounds with R^2 = H), or at 40°C (compounds with $R^2 \neq$ H) until consumption of **4**. After evaporation of the solvent under reduced pressure the products are isolated by flash chromatography.

B. *From allylic γ-hydroxyphosphonates* **2**. *General Procedure 4 (GP4)*: To a solution of **2** (10.0 mmol) and TPP (3.40 g, 13 mmol) in dry toluene (50 ml) is added under Ar atmosphere with stirring at −20°C a solution of **3** (13 mmol) in toluene (20 ml) rapidly and then dropwise a solution of DEAD (2.26 g, 13.0 mmol) in toluene (20 ml). Stirring is continued at the same temperature until consumption of **2**. The solvent is evaporated, the residue is dried at 0.01 Torr, then treated with dry Et_2O (7–10 ml), and stored at −20°C for 1 h. TPPO and diethyl hydrazo-1,2-dicarboxylate are then filtered off, the filtrate is evaporated and the products are purified by flash chromatography.

Dimethyl {3-[(tert-butoxycarbonyl)(tert-butoxycarbonyloxy)amino]-1-propenyl}phosphonate (**5a**): **4a**

(448 mg, 2.0 mmol) was caused to react with **3a** (466 mg, 2.0 mmol) according to *GP3* for 2 h at r.t. Flash chromatography (60 g silica gel, CH_2Cl_2/EtOAc, 7:3, afforded sequentially (*Z*)-**5a** (91 mg, 12%, R_f = 0.39, yellowish oil), and (*E*)-**5a** [650 mg, 85%, R_f = 0.29, colorless crystals, m.p. 60–64°C from Et_2O/PE (40°C)].

Dimethyl {3-[(tert-butoxycarbonyl)(tert-butoxycarbonyloxy)amino]-1-butenyl} phosphonate (**5c**): **4c** (1.19 g, 5.0 mmol) was caused to react with **3a** according to *GP3* for 3 h at 40°C (TLC control with CH_2Cl_2/EtOAc, 7:3). Flash chromatography (120 g silica gel, hexanes/acetone, 4:1) yielded sequentially (*Z*)-**5c** (R_f = 0.35, 50 mg, 2%), (*E*)-**5c** [R_f = 0.24, 1.70 g, 86%, with PE (40°C) colorless crystals, m.p. 43–45°C], and *dimethyl (E)-(3-methoxy-1-butenyl)phosphonate* (R_f = 0.15). The latter was separated from traces of TPPO by Kugelrohr distillation (bath temp. 80–90°C/0.01 Torr) to yield 46 mg (4.7%) of an analytical sample [^{1}H-NMR ($CDCl_3$): δ = 1.23 (d, J = 6.9 Hz, 3H, C$\underline{H}_3$CH), 3.28 (s, 3H, OCH_3), 3.69 (2d, J = 10.8 Hz, each 3H, $POCH_3$), 3.85 (m_c, 1H, 3-H), 5.80 (ddd, $J_{1,3} \approx 1.5$, $J_{1,2}$ = 17.2, $J_{1,P}$ = 20.7 Hz, 1H, 1-H), 6.66 (ddd, $J_{2,3}$ = 5.4, $J_{2,1}$ = 17.2, $J_{2,P}$ = 22.2 Hz, 1H, 2-H).—^{13}C-NMR ($CDCl_3$): δ = 20.01 ($^5J_{HP}$ = 2.0 Hz, C$\underline{H}_3$CH), 52.24, 52.28 (2d, J = 5.9 Hz, P—OCH_3), 56.62 (OCH_3), 76.94 ($^3J_{PC}$ = 21.8 Hz, C-3), 115.08 ($^1J_{PC}$ = 188.5 Hz, P—C), 154.28 ($^2J_{PC}$ = 4.3 Hz, C-2).—MS (70 eV): m/z (%) = 194 (M^+, 3), 179 (100), 163 (32), 147 (59)].

Diisopropyl (E)-{3-[(tert-Butoxycarbonyl)(tert-butoxycarbonyloxy)amino]-1-butenyl} phosphonate [(*E*)-**5d**]

A. **4d** (882 mg, 3.0 mmol) was caused to react with **3a** for 3.5 h at 40°C according to *GP3*. Flash chromatography (60 g silica gel, Et_2O) afforded 941 mg (70%) (*E*)-**5d** [R_f = 0.38, with PE (40°C) colorless crystals, m.p. 66°C].

B. **2d** (236 mg, 1.0 mmol) was caused to react with **3a** under the conditions of *GP4* (reaction time 1.5 h). Flash chromatography (50 g silica gel, Et_2O) afforded 409 mg (91%) (*E*)-**5d**.

Diisopropyl (E)-{3-[(tert-butoxycarbonyl)(tert-butoxycarbonyloxy)amino]-3-phenyl-1-propenyl} phosphonate [(*E*)-**5e**]: **4e** (1.78 g, 5.0 mmol) was caused to react with **3a** according to *GP3* for 2.5 h at 40°C. The product was purified by flash chromatography (150 g silica gel, CH_2Cl_2/EtOAc, 9:1, R_f = 0.17) and crystallization with PE (40°C). Yield 2.28 g (89%), m.p. 54–56°C.

Diethyl (E)-{3-[(tert-Butoxycarbonyl)(tert-butoxycarbonyloxy)amino]-1-methyl-1-pentenyl} phosphonate [(*E*)-**5f**]

1. *Diethyl (E)-(1-methyl-3-oxo-1-pentenyl)phosphonate*: Diethyl (1-oxoethyl)phosphonate and (2-oxobutylidene)triphenylphosphorane[41] (each 30 mmol) were caused to react in dry toluene (150 ml) for 9 h at 90°C according to the protocol given in Reference 22. Purification by flash chromatography (CH_2Cl_2/acetone, 15:1) and subsequent Kugelrohr distillation (bath temp. 90–100°C/0.01 Torr) afforded 7.70 g (92%) as a pale yellow oil.—^{1}H-NMR ($CDCl_3$): δ = 1.12 (t, J = 6.9 Hz, 3H, $COCH_2C\underline{H}_3$), 1.34 (t, J = 6.9 Hz, 6H, $POCH_2C\underline{H}_3$), 2.19 (dd, J_{HH} = 1.5, J_{HP} = 15.7 Hz, 3H, $PCCH_3$), 2.58 (q, J = 6.9 Hz, $COCH_2$), 4.12 (m_c, 4H, $POCH_2$), 6.98 (qd, J_{HH} = 1.5, $^3J_{HP}$ = 24.6 Hz, 1H, 2-H).—^{13}C-NMR ($CDCl_3$): δ = 7.43 ($COCH_2\underline{C}H_3$), 14.65 ($^2J_{PC}$ = 6.8 Hz, P—C—$\underline{C}H_3$), 16.21 (J_{PC} = 6.1 Hz, $POCH_2\underline{C}H_3$), 37.72 ($^4J_{PC}$ = 2.4 Hz, $CO\underline{C}H_2$), 62.15 (J_{PC} = 5.7 Hz, $POCH_2$), 136.12 ($^2J_{PC}$ = 9.1 Hz, C-2), 140.46 ($^1J_{PC}$ = 169.4 Hz, PC), 201.43 ($^3J_{PC}$ = 22.8 Hz, CO).

2. *Diethyl (E)-(3-hydroxy-1-methyl-1-pentenyl)phosphonate* (**2f**): The above 3-oxophosphonate was caused to react with sodium borohydride as described previously for the synthesis of **2d**[13a] to give **2f** quantitatively as a colorless oil (TLC: CH_2Cl_2/EtOAc, 1:9, R_f = 0.17).—^{1}H-NMR ($CDCl_3$): δ = 0.93 (t, J = 7.4 Hz, 3H, C—$CH_2C\underline{H}_3$), 1.32 (t, J = 6.9 Hz, 6H, $POCH_2C\underline{H}_3$), 1.53, 1.68 (2m_c, each 1H, C—CH_2), 1.83 (dd, J_{HH} = 1.5, J_{HP} = 14.7 Hz, 3H, $PCCH_3$), 3.54 (br.d, $J \approx 5$ Hz, 1H, OH), 4.05 (m_c, 4H, $POCH_2$), 4.36 (m_c, 1H, C$\underline{H}$OH), 6.48 (qdd, $^4J_{HH}$ = 1.5, $J_{2,3}$ = 8.4, $J_{2,P}$ = 24.1 Hz, 1H, 2-H).—^{13}C-NMR ($CDCl_3$): δ = 9.48 (C—$CH_2\underline{C}H_3$), 12.82 ($^2J_{PC}$ = 10.1 Hz, P—C—$\underline{C}H_3$), 16.20 (J_{PC} = 6.3 Hz, $POCH_2\underline{C}H_3$), 29.59 ($^4J_{PC}$ = 1.2 Hz, C—$\underline{C}H_2$), 61.63, 61.66 (J_{PC} = 5.4 Hz, $POCH_2$), 69.17 ($^3J_{PC}$ = 20.9 Hz, C-3), 124.84 ($^1J_{PC}$ = 177.3 Hz, P—C), 148.36 ($^2J_{PC}$ = 8.3 Hz, C-2).

3. (*E*)-**5f**: **2f** (944 mg, 4.0 mmol) was caused to react with **3a** according to *GP4* for 1 h at −20°C. The product was isolated by flash chromatography (100 g silica gel, Et_2O, R_f = 0.70) as a colorless oil. Yield 1.72 g (95%).

Dimethyl {3-[(tert-butoxycarbonyl)(tert-butoxycarbonyloxy)amino]-1-cyclopenten-1-yl} phosphonate (**5g**): **2g**[40] (768 mg, 4.0 mmol) was caused to react with **3a** according to *GP4*. Flash chromatography (80 g silica gel, elution with Et_2O until the appearance of diethyl hydrazo-1,2-dicarboxylate, followed by CH_2Cl_2/acetone, 9:1) yielded **5g** [1.41 g, 87%, with PE (40°C) colorless crystals, m.p. 67–69°C].

TABLE V

Compounds **5–8** prepared

	Molecular Formula	Elemental analysis calc. (found)			m.p. (°C)	IR ν (cm^{-1})[a]		
		% C	% H	% N		OCO	NCO	C=C
(*Z*)-**5a**	$C_{15}H_{28}NO_8P$ (381.4)	47.23 (47.77	7.41 7.29	3.67 3.48)	oil	1784	1714	1633
(*E*)-**5a**	$C_{15}H_{28}NO_8P$ (381.4)	47.23 (47.58	7.41 7.30	3.63 3.53)	60-64	1786	1724	1642
(*Z*)-**5c**	$C_{16}H_{30}NO_8P$ (395.5)	48.59 (48.93	7.66 7.51	3.54 3.41)	oil	1789	1716	1629
(*E*)-**5c**	$C_{16}H_{30}NO_8P$ (395.5)	48.59 (48.83	7.66 7.59	3.54 3.49)	43-45	1790	1714	1639
(*E*)-**5d**	$C_{20}H_{38}NO_8P$ (541.6)	53.19 (53.59	8.50 8.54	3.10 3.14)	66	1790	1715	1637
(*E*)-**5e**	$C_{25}H_{40}NO_8P$ (513.6)	59.04 (58.73	7.87 7.94	2.73 2.71)	54-56	1793	1712	1636
(*E*)-**5f**	$C_{20}H_{38}NO_8P$ (451.6)	53.19 (53.58	8.50 8.47	3.10 3.30)	oil	1790	1716	1640
5g	$C_{17}H_{30}NO_8P$ (407.5)	50.10 (50.33	7.44 7.42	3.44 3.42)	67-69	1782	1718	1618
5h	$C_{18}H_{32}NO_8P$ (421.5)	51.29 (51.64	7.67 7.74	3.32 3.31)	64-66	1789	1714	1637
5i	$C_{19}H_{34}NO_8P$ (435.5)	52.39 (51.97	7.88 7.76	3.22 3.01)	78-79	1791	1705	1640
(*Z*)-**6b**	$C_{13}H_{24}NO_8P$ (353.4)	44.18 (44.36	6.86 7.08	3.96 3.79)	oil	1798	1732	1633
(*E*)-**6b**	$C_{13}H_{24}NO_8P$ (353.4)	44.18 (44.58	6.86 7.12	3.96 3.51)	oil	1794	1734	1639
(*E*)-**6d**	$C_{14}H_{26}NO_8P$ (367.4)	45.77 (45.37	7.15 7.41	3.81 3.61)	oil	1799	1732	1637
6h[b]	$C_{12}H_{20}NO_8P$ (337.3)				oil	1797	1732	1641
(*Z*)-**7a**	$C_{17}H_{26}NO_6P$ (371.4)	54.97 (54.63	707 6.88	3.77 3.61)	oil	-	1698	1632
(*E*)-**7a**	$C_{17}H_{26}NO_6P$ (371.4)	54.97 (54.80	7.07 6.78	3.77 3.52)	oil	-	1698	1641
(*E*)-**7d**	$C_{22}H_{36}NO_6P$ (441.6)	59.84 (60.07	8.23 8.01	3.17 2.98)	<20	-	1707	1634
(*E*)-**8c**	$C_{10}H_{18}NO_6P$ (279.3)	43.00 (42.78	6.51 6.33	5.02 4.78)	oil	1798	1681	-
8h[c]	$C_{12}H_{20}NO_6P$ (305.3)				oil	1795	1676	-

[a]Nujol for compounds (*E*)-**5a**, **c**, **d**, **5g–i**, (*E*)-**8c**; film on Si-plates for (*Z*)-**5a**, **c**, (*E*)-**5f**, **6b**, (*E*)-**6d**, **6h**, **7a**, (*E*)-**7d**, **8h**.

[b]**6h** was immediately converted to **13h**.

[c]**8h** was immediately converted to **12h**.

TABLE VI

^{1}H-NMR spectra of N,O-diprotected compounds **5–8** [δ, J (Hz)][a]

	1-H	2-H	3-H	$J_{1,P}$	$J_{1,2}$	$J_{1,3}$	$J_{2,P}$	$J_{2,3}$	R^2 - R^5
(*Z*)-**5a**	5.71	6.60	4.68	17.2	13.3	2.0	51.7	6.4	1.47, 1.50 [2s, $C(CH_3)_3$]
(*E*)-**5a**	5.91	6.71	4.32	19.2	17.2	1.5	22.1	4.9	1.45, 1.49 [2s, $C(CH_3)_3$]
(*Z*)-**5c**	5.36	6.51	5.95	16.2	13.2	1	51.4	9.1	1.35, 1.39 [2s, $C(CH_3)_3$], 1.39 (d, 6.9, $C\underline{H}_3CH$)
(*E*)-**5c**	5.80	6.78	4.76	18.1	17.3	1.5	22.0	5.2	1.15 (d, 6.9, $C\underline{H}_3CH$), 1.34, 1.36 [2s, $C(CH_3)_3$]
(*E*)-**5d**	5.91	6.83	4.80	18	17.2	1.5	22.2	5.0	1.20 (d, 7.0, $C\underline{H}_3CH$), 1.35, 1.38 [2s, $C(CH_3)_3$]
(*E*)-**5e**	6.00	7.12	5.88	17.9	17.3	1.5	21.7	5.8	1.28, 1.34 [2s, $C(CH_3)_3$], 6.95-7.08,7.31-7.35 ($5H_{arom}$)
(*E*)-**5f**	-	6.68[b]	4.88	-	-	-	23.1	8.8	0.86 (t, 7.4, C-$CH_2C\underline{H}_3$), 1.36, 1.37 [2s, $C(CH_3)_3$], 1.50, 1.81 (2dquin, J_{AB} = 13.7, $J_{AH} \approx J_{BH} \approx 7$, C-$C\underline{H}_2CH_3$) 1.93 (dd, $^4J_{HH}$ = 1.6, $^3J_{HP}$ = 14.3, $PCCH_3$)
5g	-	6.50	5.30	-	-	-	11.0	2.2	1.33, 1.38 [2s, $C(CH_3)_3$], 1.97 (br.q, 7, 2H), 2.28, 2.57 ($2m_c$, each 1H) [CH_2]
5h	-	6.78	4.78	-	-	-	22	2	1.35, 1.38 [2s, $C(CH_3)_3$], 1.58 (m, 1H), 1.73-1.79 (m, 2H), 2.05 (m,1H), 2.09 (m, 2H) [CH_2]
5i	-	7[c]	4.95	-	-	-	25[c]	-	1.37, 1.39 [2s, $C(CH_3)_3$], 1.20 (m_c, 1H), 1.3-1.5 (m, 2H), 1.65-1.85 (m, 2H), 1.88- 1.97 (m, 1H), 2.05 (m, 1H), 2.45 (m_c, 1H) [CH_2]
(*Z*)-**6b**	5.76	6.47	4.80	16.2	13.3	1.5	51.2	6.4	3.79, 3.88 (2s, CO_2CH_3)
(*E*)-**6b**	5.93	6.65	4.37	18.7	17.2	1.5	22.2	4.9	3.79, 3.88 (2s, CO_2CH_3)
(*E*)-**6d**	5.84	6.65	4.89	-[d]	17.2	-[d]	22.1	4.9	1.34 (d, 6.9, $C\underline{H}_3CH$), 3.77, 3.86 (2s, CO_2CH_3)
6h	-	6.51	4.81	-	-	-	22.2	-[d]	1.64 (m_c, 2H), 1.80-2.00 (m, 2H), 2.13 (m_c, 2H) [CH_2], 3.75, 3.82 (2s, CO_2CH_3)
(*Z*)-**7a**	5.59	6.46	4.51[e]	17.7	13.3	1.5	52.2	6.4	1.42 [s, $C(CH_3)_3$], 4.78 (s, OCH_2), 7.23-7.29 ($3H_{arom}$), 7.31-7.35 ($2H_{arom}$)
(*E*)-**7a**	5.77	6.70	4.09[f]	19.7	17.2	1.5	21.7	5.4	1.47 [s, $C(CH_3)_3$], 4.82 (s, OCH_2), 7.30-7.37 (m, $5H_{arom}$)
(*E*)-**7d**	5.78	6.76	4.69	18.7	17.2	1.5	22.2	5.4	1.34 (d, 6.9, $C\underline{H}_3CH$), 1.49 [s, $C(CH_3)_3$], 4.79 (δ_A), 4.86 (δ_B) [J_{AB} = 9.4, OCH_2], 7.30-7.39 (m, $5H_{arom}$)
(*E*)-**8c**	5.73	6.63	5.2	18.7	17.2	1.5	22.2	4.9	1.25 (d, 6.9, $C\underline{H}_3CH$), 1.96, 2.14 ($COCH_3$)
8h	-	6.46	5.18	-	-	-	22.1	2	1.55-1.72 (m, 2H), 1.80-1.96 (m, 2H), 2.12-2.19 (m, 2H) [CH_2], 1.99, 2.14 ($COCH_3$)

[a]Solvent $CDCl_3$, 25°C for compounds **5a**, **6**, **7**, and **8**; solvent toluene-d_8, 90–100°C for compounds **5c–i**.

[b]$^4J_{HH}$ = 1.6 Hz.

[c]Signal partially overlapped with solvent signals.

[d]Not resolved.

[e]$J_{3,P}$ = 3.0 Hz.

[f]$J_{3,P}$ = 2.9 Hz.

TABLE VII

^{13}C-NMR spectra of N,O-diprotected compounds **5–8** [δ, J (Hz)][a]

	C-1	$^1J_{PC}$	C-2	$^2J_{PC}$	C-3	$^3J_{PC}$	R^2 - R^5
(*Z*)-**5a**	117.97	182.9	147.68	3.0	49.55	7.8	27.41, 27.88 [C(<u>C</u>H$_3$)$_3$], 82.69, 84.76 [<u>C</u>Me$_3$], 151.90, 154.35 [CO]
(*E*)-**5a**	118.07	188.5	146.32	5.7	52.30	24.6	27.50, 27.96 [C(<u>C</u>H$_3$)$_3$], 83.06, 85.16 [<u>C</u>Me$_3$], 152.00, 154.45 [CO]
(*Z*)-**5c**[b]	118.12	182.5	151.60	4.3	56.87	7.3	19.21 ($^4J_{PC}$ = 2.0, <u>C</u>H$_3$CH), 28.81, 29.37 [C(<u>C</u>H$_3$)$_3$], 83.07, 84.73 [<u>C</u>Me$_3$], 155.63 [CO]
(*E*)-**5c**[c]	120.20	187.1	151.32	5.0	58.49	22.9	16.91 (<u>C</u>H$_3$CH), 28.77, 29.29 [C(<u>C</u>H$_3$)$_3$], 83.34, 84.99 (<u>C</u>Me$_3$)
(*E*)-**5d**[c]	123.13	187.2	149.45	5.2	58.54	23.1	17.02 (<u>C</u>H$_3$CH), 28.81, 29.31 [C(<u>C</u>H$_3$)$_3$], 83.21, 84.85 [<u>C</u>Me$_3$]
(*E*)-**5e**	125.26	184.6	147.19	5.9	67.03	23.3	28.71, 29.23 [C(<u>C</u>H$_3$)$_3$], 83.49, 84.95 [<u>C</u>Me$_3$], 129.27, 129.71 (*o*-, *m*-CH), 129.68 (*i*-C), 130.13 (*p*-CH), 153.58, 155.80 [CO]
(*E*)-**5f**[d]	-	-	142.25	br.s	-	-	11.47 (C-CH$_2$<u>C</u>H$_3$), 14.56 ($^2J_{PC}$ = 9.6, PC<u>C</u>H$_3$), 26.32 (br. s, C-<u>C</u>H$_2$CH$_3$), 28.55, 29.08 [C(<u>C</u>H$_3$)$_3$], 82.81, 84.66 [<u>C</u>Me$_3$], 153.86 (CO)
5g	139.14	187.2	143.90	13.9	67.88	22.9	28.77, 29.34 [C(<u>C</u>H$_3$)$_3$], 29.17 (10.2), 33.71 (12.5) [CH$_2$], 83.05, 85.02 [<u>C</u>Me$_3$], 154.25, 155.33 [CO]
5h	133.98	176.6	141.32	9.0	57.53	19.7	22.17 (10.9), 25.65 (8.2), 26.91 (s) [CH$_2$], 83.11, 84.97 [<u>C</u>Me$_3$], 154.15, 155.59 [CO]
5i	134.13	177.4	148.51	10.1	63.17	25.4	27.20 (7.2), 29.49 (9.3), 29.62 (s), 32.09 (s) [CH$_2$], 28.82, 29.34 [<u>C</u>(CH$_3$)$_3$], 83.28, 85.00 [<u>C</u>Me$_3$], 154.15, 155.86 [CO]
(*Z*)-**6b**	121.89	182.6	144.40	2.8	49.80	7.8	53.83, 56.11 [CO$_2$<u>C</u>H$_3$], 154.61, 155.93 [CO]
(*E*)-**6b**	121.96	188.2	143.01	5.9	52.54	24.9	53.82, 56.06 [CO$_2$<u>C</u>H$_3$], 154.37, 155.70 [CO]
(*E*)-**6d**	120.91	184.0	147.49	5.1	57.42	23.2	15.57 (br s, <u>C</u>H$_3$CH), 53.87, 56.13 [CO$_2$<u>C</u>H$_3$], 154.87, 156.00 [CO]
6h[e]	-	-	-	-	56.68	20.1	20.65 (11.2), 23.80 (8.4), 24.70 (br. s) [CH$_2$], 53.89, 56.15 [CO$_2$<u>C</u>H$_3$], 154.93, 155.97 [CO]
(*Z*)-**7a**	117.43	183.2	148.95	3.7	48.82	7.8	28.17 [C(<u>C</u>H$_3$)$_3$], 76.88 (OCH$_2$), 81.82 (<u>C</u>Me$_3$), 128.30, 129.50 (*o*-, *m*-CH), 128.47 (*p*-CH), 135.23 (*i*-C), 156.28 (CO)
(*E*)-**7a**	117.93	188.4	147.43	5.3	52.49	24.5	28.14 [C(<u>C</u>H$_3$)$_3$], 77.30 (OCH$_2$), 81.99 (<u>C</u>Me$_3$), 128.38, 129.31 (*o*-, *m*-CH), 128.54 (*p*-CH), 135.29 (*i*-C), 156.23 (CO)
(*E*)-**7d**	119.65	187.6	149.76	4.9	57.16	23.1	15.96 (<u>C</u>H$_3$CH), 28.21 [C(<u>C</u>H$_3$)$_3$], 78.57 (OCH$_2$), 81.85 (<u>C</u>Me$_3$), 128.30, 129.20 (*o*-, *m*-CH), 128.41 (*p*-CH), 135.30 (*i*-C), 156.73 (CO)
(*E*)-**8c**	120.44	187.3	151.01	5.1	56.54	23.3	16.88 (<u>C</u>H$_3$CH), 18.40, 21.25 [CO<u>C</u>H$_3$], 169.46, 171.26 (CO)
8h[f]	-	-	139.88	br.s	-	-	18.18, 20.56 (CO<u>C</u>H$_3$), 20.69 (11.2), 23.78 (8.7), 25.21 (s) [CH$_2$]

[a]Solvent $CDCl_3$, 25°C for compounds **5a**, **6**, **7**, **8h**; solvent toluene-d_8, 90–100°C for compounds **5c–i**, **8c**.

[b]One CO-carbon missing.

[c]No CO-signals registered.

[d]No signals detected for C-1, C-3 and one CO.

[e]No signals detected for C-1 and C-2 at r.t.

[f]No signals registered at r.t. for C-1, C-3, and both carbonyl carbons.

Dimethyl {3-[(tert-butoxycarbonyl)(tert-butoxycarbonyloxy)amino]-1-cyclohexen-1-yl}phosphonate (**5h**): **2h**[40] (640 mg, 3.1 mmol) was caused to react with **3a** according to *GP4*. Reaction time 1.5 h at −20°C. Flash chromatography (80g silica gel, elution with Et_2O until the appearance of diethyl hydrazo-1,2-dicarboxylate, followed by hexanes/acetone, 7:3) yielded **5h** (1.19 g, 91%), with PE (40°C) colorless crystals, m.p. 64–66°C.

Dimethyl {3-[(tert-butoxycarbonyl)(tert-butoxycarbonyloxy)amino]-1-cyclohepten-1-yl}phosphonate (**5i**): **2i** (220 mg, 1.0 mmol) was caused to react with **3a** according to *GP4*. Reaction time 4 h at −20°C; flash chromatography (20 g silica gel, Et_2O, R_f = 0.19) yielded **5i** (377 mg, 87%), with PE (40°C) colorless crystals, m.p. 78–79°C.

Diisopropyl {3-[(methoxycarbonyl)(methoxycarbonyloxy)amino]-1-propenyl}phosphonate (**6b**): **4b** (560 mg, 2.0 mmol) was caused to react with **3b** for 1.5 h at r.t. according to *GP3*, using 70 mg (3 mol%) $Pd(Ph_3P)_4$. Flash chromatography (50 g silica gel, CH_2Cl_2/EtOAc, 1:1) yielded sequentially 54 mg (7.6%) (*Z*)-**6b** (oil, R_f = 0.52), and 633 mg (90%) (*E*)-**6b** (oil, R_f = 0.28).

Diisopropyl (E)-{3-[(Methoxycarbonyl)(methoxycarbonyloxy)amino]-1-butenyl}phosphonate (**6d**)

A. **4d** (294 mg, 1.0 mmol) was caused to react with **3b** for 3.5 h at 40°C according to *GP3*. Flash chromatography (30 g silica gel, hexanes/acetone, 4:1) yielded sequentially *diisopropyl (E)-(1,3-butadienyl)phosphonate* (R_f = 0.30, 24 mg, 11%) as a colorless oil [^{1}H-NMR ($CDCl_3$): δ = 1.23 (d, *J* = 6.4 Hz, 6H), 1.27 (d, *J* = 5.9 Hz, 6H) [POCH($C\underline{H}_3$)$_2$], 4.60 (m_c, 2H, POCH), 5.37 (m_c, $J_{4b,3}$ = 10.8 Hz, 1H, 4-H_b), 5.47 (d, $J_{4a,3}$ = 17.2 Hz, 1H, 4-H_a), 5.67 (br dd, $J_{1,2}$ = 16.7, $J_{1,P}$ = 18.7 Hz, 1H, 1-H), 6.34 (m_c, 1H, 3-H), 6.98 (ddd, $J_{2,3}$ = 10.8, $J_{2,1}$ = 16.7, $J_{2,P}$ = 20.7 Hz, 1H, 2-H).— ^{13}C-NMR ($CDCl_3$): δ = 23.92 (J_{PC} = 4.6 Hz), 24.02 (J_{PC} = 4.0 Hz) [POCH($\underline{C}H_3$)$_2$], 70.35 (J_{PC} = 5.6 Hz, POCH), 119.77 ($^1J_{PC}$ = 191.0 Hz, C-1), 124.38 (C-4), 135.83 ($^3J_{PC}$ = 26.8 Hz, C-3), 147.85 ($^2J_{PC}$ = 5.8, C-2)], and (*E*)-**6d** (275 mg, 75%, R_f = 0.10) as a viscous oil.

B. **2d** (236 mg, 1.0 mmol) was caused to react with **3b** under the conditions of *GP4*. Reaction time 45 min at −20°C. Flash chromatography (25 g silica gel, Et_2O until the elution of diethyl hydrazo-1,2-dicarboxylate and then CH_2Cl_2/acetone, 9:1) yielded (*E*)-**6d** (336 mg, 91%), which contained 10–15% TPPO and was converted to **13d** without further purification.

Dimethyl {3-[(methoxycarbonyl)(methoxycarbonyloxy)amino]-1-cyclohexen-1-yl}phosphonate (**6h**): **2h** (412 mg, 2.0 mmol) was caused to react with **3b** according to *GP4*. Reaction time 1 h at −20°C. Flash chromatography (40 g silica gel, Et_2O for the elution of diethyl hydrazo-1,2-dicarboxylate, then CH_2Cl_2/acetone, 2:1 for the elution of **6h**, R_f = 0.59) yielded **6h** (600 mg, 89%) as an oil, which after spectroscopical investigation was converted to **13h**.

Dimethyl {3-[(N-benzyloxy-N-tert-butoxycarbonyl)amino]-1-propenyl}phosphonate (**7a**): **4a** (672 mg, 3.0 mmol) was caused to react with **3c** for 1.5 h at r.t., according to *GP3*. Flash chromatography (75 g silica gel, CH_2Cl_2/acetone, 15:1 for (*Z*)-**7a**, and then CH_2Cl_2/acetone, 9:1) afforded (*Z*)-**7a** (168 mg, 15%, R_f = 0.31), and (*E*)-**7a** (545 mg, 49%, R_f = 0.16), both as viscous oils.

Diisopropyl (E)-{3-[(N-benzyloxy-N-tert-butoxycarbonyl)amino]-1-butenyl}phosphonate (**7d**): **2d** (236 mg, 1.0 mmol) was caused to react with **3c** under the conditions of *GP4* for 1 h at −20°C, then 1 h at r.t. Flash chromatography (45 g silica gel, Et_2O until the elution of diethyl hydrazo-1,2-dicarboxylate, then CH_2Cl_2/EtOAc, 7:3 to 1:9) yielded sequentially (*E*)-**7d** (R_f = 0.50, CH_2Cl_2/EtOAc, 7:3, 125 mg, 28%, forming colorless crystals at −20°C) and *diethyl [1-(E)-(3-diisopropoxyphosphonyl-1-methyl-2-propenyl)-1,2-hydrazine]dicarboxylate* [R_f = 0.11, CH_2Cl_2/EtOAc, 7:3, 170 mg, 43%, oil; ^{1}H-NMR (toluene-d_8, 100°C): δ = 1.04, 1.05 (2t, *J* = 7.1 Hz, each 3H, $CO_2CH_2C\underline{H}_3$), 1.19 (d, *J* = 6.0 Hz, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 6H) [POCH($C\underline{H}_3$)$_2$], 1.19 (d, *J* = 7.5 Hz, 3H, $C\underline{H}_3$CH), 4.01 (m_c, 4H, CO_2CH_2), 4.67 (m_c, 2H, POCH), 4.83 (br m, 1H, CHN), 5.78 (ddd, $J_{1,3}$ ≈ 1.5, $J_{1,2}$ = 17.3, $J_{1,P}$ = 18.7 Hz, 1H, 1-H), 6.90 (ddd, $J_{2,3}$ = 5.5, $J_{2,1}$ = 17.3, $J_{2,P}$ = 22.3 Hz, 1H, 2-H), 7.16 (br s, 1H, NH).— ^{13}C-NMR (toluene-d_8, 100°C): δ = 15.63, 16.49, 17.60 (CH_3), 25.12 (J_{PC} = 3.8 Hz, 1C), 25.16 (J_{PC} = 4.2 Hz, 1C), 25.26 (J_{PC} = 4.1 Hz, 2C) [POCH($\underline{C}H_3$)$_2$], 57.56 ($^3J_{PC}$ = 23.6 Hz, CHN), 62.68, 63.28 ($CO_2\underline{C}H_2$), 71.24 (J_{PC} = 3.6 Hz, POCH), 121.73 ($^1J_{PC}$ = 189.2 Hz, PC), 151.72 (J_{PC} = 4.9 Hz, C-2), 156.75, 158.14 (CO)].

Dimethyl (E)-{[3-(N-Acetyl-N-acetyloxy)amino]-1-butenyl}phosphonate [(*E*)-**8c**]

A. **4c** (544 mg, 2.28 mmol) was caused to react with **3d** for 1.5 h at 40°C according to *GP3*. Flash chromatography (70 g silica gel, CH_2Cl_2/acetone, 4:1) yielded sequentially *dimethyl (E)-(1,3-*

butadienyl)phosphonate (66 mg, R_f = 0.48, 18%, identified by ^{1}H-NMR spectroscopy[42]), and (*E*)-**8c** (R_f = 0.26, 368 mg, 58%, oil).

B. A solution of (*E*)-**5c** (395 mg, 1.0 mmol) in TFA/CH_2Cl_2 (each 2 ml) was left at r.t. for 6 h, then evaporated and dried for 1 h at 0.01 Torr. To a stirred solution of the residue in dry CH_2Cl_2 (5 ml) was added $NaHCO_3$ (ca. 1.5 g), and stirring was continued for 45 min. Then Ac_2O (1 ml) was added and the reaction monitored by TLC (EtOAc/MeOH, 19:1). After 4 h [TLC showed invariably (*E*)-**8c** (R_f = 0.33) together with a second reaction product with very similar polarity][30] the solids were filtered off, the filtrate was evaporated in vacuo and the residue caused to react with Ac_2O/pyridine (each 1 ml) for 3 h at r.t. Evaporation at reduced pressure, followed by flash chromatography (15 g silica gel, EtOAc/MeOH, 19:1) afforded then (*E*)-**8c** (225 mg, 81%) as the sole product.

Dimethyl {[3-(N-acetyl-N-acetyloxy)amino]-1-cyclohexen-1-yl}phosphonate (**8h**): A solution of **5h** (210 mg, 0.5 mmol) in TFA/CH_2Cl_2 (each 1 ml) was left at r.t. for 6 h, then evaporated and dried thoroughly at 0.01 Torr. To a stirred solution of the residue in dry CH_2Cl_2 (5 ml) was added $NaHCO_3$ (0.5 g) and stirring was continued for 45 min. Then Ac_2O (1 ml) was added and stirring continued for 2.5 h at r.t. Then the solids were filtered off, the filtrate was evaporated at reduced pressure. The residue was dried at 0.01 Torr and caused to react with Ac_2O/pyridine (each 1 ml) for 16 h at r.t. After evaporation and flash chromatography (6 g silica gel, EtOAc/MeOH, 19: 1, R_f = 0.27) **8h** (123 mg, 81%) was isolated as a colorless, viscous oil, which was immediately converted to **12h**.

[3-(N-Hydroxyamino)-1-alkenyl]phosphonic Acids **9** *from Compounds* **5**

A. *Deprotection with boiling HCl. General Procedure 5 (GP5)*: A suspension of **5** (1 mmol) in 6 M HCl (6 ml) is refluxed for 6 h, then cooled to r.t., diluted with water (10 ml), and extracted with toluene (3 × 5 ml) and Et_2O (5 ml). The aqueous solution is evaporated at reduced pressure. The residue is dried at 0.01 Torr, then dissolved in a minimum amount of MeOH, and adjusted to pH 4–5 by the dropwise addition of propylene oxide under vigorous stirring. The solid is filtered off after 15 min and dried for 5 h at 50°C. Analytically pure samples are obtained upon recrystallization from H_2O/MeOH.

B. *Deprotection with TMSBr/HBr/H$_2$O. General Procedure 6 (GP6)*: A suspension of **5** (1 mmol) in TMSBr (ca. 1.5 ml, 10 mmol) is stirred for 24 h at r.t. and then evaporated at reduced pressure. To the residue is added H_2O (10 ml) and aqueous HBr (48%, 1 drop), and stirring is continued for 24 h at r.t. The solution is then washed with toluene (2 × 2 ml) and Et_2O (5 ml), and then evaporated at reduced pressure. The residue is dried at 0.01 Torr for 1 h, and then treated with propylene oxide as given above to liberate **9**.

(E)-[3-(N-Hydroxyamino)-1-butenyl]phosphonic Acid [(*E*)-**9c**]

A. *From (E)-***5c** *by GP5*: Yield 90%, m.p. 150–152°C (dec.).

B. *From (E)-***5d** *by GP6*: Yield 73%, m.p. 175°C (dec.), after recrystallization from H_2O/MeOH.—^{1}H-NMR (D_2O): δ = 1.54 (d, J = 6.9 Hz, 3H, C$\underline{H}_3$CH), 4.26 (br quin, $J \approx 7$ Hz, 1H, CHN), 6.31 (br t, $J_{1,2} \approx J_{1,P} \approx 17$ Hz, 1H, 1-H), 6.45 (ddd, $J_{2,3}$ = 6.9, $J_{2,1}$ = 17.2, $J_{2,P}$ = 20.2 Hz, 1H, 2-H).—^{13}C-NMR (D_2O): δ = 17.77 (CH_3), 63.42 ($^3J_{PC}$ = 22.5 Hz, C-3), 134.93 ($^1J_{PC}$ = 173.3 Hz, PC), 140.63 ($^2J_{PC}$ = 4.1 Hz, C-2).

$C_4H_{10}NO_4P$ (167.1) Calc.: C 28.75 H 6.04 N 8.38
found: C 29.07 H 5.82 N 8.22

(E)-[3-(N-Hydroxyamino)-1-methyl-1-pentenyl]phosphonic acid (**9f**) *from* **5f** *by GP6*: Yield 71%, m.p. 194–197°C (dec.) after recrystallization from H_2O/MeOH.—^{1}H-NMR (D_2O): δ = 1.04 (t, J = 7.4 Hz, 3H, C$\underline{H}_3$CH$_2$), 1.75, 2.05 (2m$_c$, each 1H, C$\underline{H}_2$CH$_3$), 2.02 (d, J_{HP} = 13.8 Hz, 3H, P—C—CH$_3$), 4.35 (m$_c$, 1H, CHN), 6.12 (dd, $J_{2,3}$ = 9.8, $J_{2,P}$ = 21.2 Hz, 1H, 2-H).—^{13}C-NMR (D_2O): δ = 13.05 (C$\underline{H}_3$CH$_2$), 17.90 ($^2J_{PC}$ = 10.1 Hz, PC$\underline{C}$H$_3$), 26.55 (C$\underline{H}_2$CH$_3$), 64.92 ($^3J_{PC}$ = 19.2 Hz, C-3), 132.92 ($^2J_{PC}$ = 10.5 Hz, C-2), 145.91 ($^1J_{PC}$ = 166.5 Hz, PC).

$C_6H_{14}NO_4P$ (195.2) Calc.: C 36.92 H 7.24 N 7.18
found: C 37.30 H 7.10 N 7.18

[3-(N-Hydroxyamino)-1-cyclohexen-1-yl]phosphonic acid (**9h**) *from* **5h** *by GP5*: Yield 87%, m.p. 200–204°C (dec.).—^{1}H-NMR (D_2O): δ = 1.72–1.93 (m, 2H), 1.93–2.04 (m, 1H), 2.14–2.24 (m, 1H), 2.38 (m$_c$, 2H) [CH_2], 4.24 (m$_c$, 1H, 3-H), 6.44 (br d, J_{HP} = 19.7 Hz, 1H, 2-H).—^{13}C-NMR (D_2O): δ = 23.06 (J_{PC} = 9.8 Hz), 26.56 (s), 28.77 (J_{PC} = 8.7 Hz) [CH_2], 61.45 ($^3J_{PC}$ = 18.3 Hz, CHN), 129.44 ($^2J_{PC}$ = 10.0 Hz, C-2), 147.80 ($^1J_{PC}$ = 168.8 Hz, PC).

$C_6H_{12}NO_4P$ (193.2) Calc.: C 37.30 H 6.27 N 7.25
found: C 37.58 H 6.20 N 7.13

N-Hydroxyureas **10**. *General Procedure 7 (GP7)*: A solution of **5** (1.0 mmol) in TFA/CH_2Cl_2 (each 2 ml) is left at r.t. for 6 h, then evaporated and dried at 0.01 Torr for 1 h. To a solution of the remaining trifluoroacetate **11** in THF/H_2O (each 2 ml) is added KOCN (100 mg, 1.24 mmol) and stirring is continued at r.t. for 18 h. Then the mixture is evaporated to dryness and the product isolated by flash chromatography.

[*N-(E)-(3-Diisopropoxyphosphonyl-2-propenyl)-N-hydroxy*]*urea* (**10b**): Flash chromatography (25 g silica gel, CH_2Cl_2/MeOH, 15:1, R_f = 0.14), yield 65%, m.p. 110°C (EtOAc).

[*N-(E)-3-(Diisopropoxyphosphonyl-1-methyl-2-propenyl)-N-hydroxy*]*urea* (**10d**): Flash chromatography (25 g silica gel, CH_2Cl_2/MeOH, 12:1, R_f = 0.54), yield 65%, colorless crystals, m.p. 131–133°C (EtOAc).

[*N-(E)-(3-Diisopropoxyphosphonyl-1-phenyl-2-propenyl)-N-hydroxy*]*urea* (**10e**): Flash chromatography (30 g silica gel, CH_2Cl_2/MeOH, 15:1, R_f = 0.25), yield 85%, colorless crystals, m.p. 143–144°C (EtOAc).

[*N-(3-Dimethyoxyphosphonyl-2-cyclohexen-1-yl)-N-hydroxy*]*urea* (**10h**): Flash chromatography (14 g silica gel, CH_2Cl_2/MeOH, 15:1, R_f = 0.46, yield 69%, m.p. 152–155°C (dec.) from MeOH/EtOAc.

Dimethyl (E)-{[3-(N-acetyl-N-hydroxy)amino]-1-butenyl}phosphonate (**12c**): To a stirred solution of (*E*)-**8c** (279 mg, 1.0 mmol) in dry MeOH (5 ml) was added at r.t. a catalytical amount of NaOMe in MeOH (sat., 2 drops). After completion of the reaction (TLC, EtOAc/MeOH, 19:1, **8c**: R_f = 0.33, **12c**: R_f = 0.20, ca 30 min), solid CO_2 was immediately added in small portions, the mixture was evaporated and the crude product purified by flash chromatography to yield **12c** (211 mg, 89%) as a colorless viscous oil.

Dimethyl {[3-(N-acetyl-N-hydroxy)amino]-1-cyclohexen-1-yl}phosphonate (**12h**): To a stirred solution of **8h** (110 mg, 0.36 mmol) in dry MeOH (2 ml) was added at r.t. a catalytical amount of NaOMe in MeOH (sat., 1 drop). After completion of the reaction (TLC, EtOAc/MeOH, 19:1, **8h**: R_f = 0.27, **12h**: R_f = 0.13, ca. 30 min) solid CO_2 was immediately added in small portions, the mixture was evaporated and the crude product purified by flash chromatography (5 g silica gel) to yield **12h** (86 mg, 91%) as colorless crystals, m.p. 116–117°C (EtOAc/Et_2O).

Dialkyl [3-[(N-Hydroxy-N-methyoxycarbonyl)amino]-1-alkenyl}phosphonates (**13**) *from compounds* **6**. *General Procedure 8 (GP8)*: To a solution of **6** (1 mmol) in MeOH (1 ml) is added at r.t. NH_3/MeOH (sat., 1 ml), and transesterification is chequed by TLC. If **6** has disappeared (10–20 min) the solvent is removed immediately[31] and **13** isolated by filtration over silica gel.

Diisopropyl (E)-{3-[N-hydroxy-N-methoxycarbonyl)amino]-1-propenyl}phosphonate (**13b**): Reaction time 15 min [TLC, CH_2Cl_2/acetone, 4:1, (*E*)-**6b**: R_f = 0.46, **13b**: R_f = 0.20]. Yield 86%, colorless crystals m.p. 50–52°C [EtOAc/PE (40°C)].

Diisopropyl (E)-{3-[N-Hydroxy-N-methoxycarbonyl)amino]-1-butenyl}phosphonate (**13d**): Reaction time, TLC, and work up as given for **13b**. Yield 85%, m.p. 62–64°C (Et_2O).

Dimethyl {3-[N-hydroxy-N-methoxycarbonyl)amino]-1-cyclohexen-1-yl}phosphonate (**13h**): Flash chromatography (CH_2Cl_2/acetone, 2:1, **6h**: R_f = 0.59, **13h**: R_f = 0.24), yield 89%, with Et_2O colorless crystals, m.p. 120–122°C.

Dimethyl (E)-{3-[(N-acetyl-N-benzyloxy)amino]-1-propenyl}phosphonate (**14a**): A solution of (*E*)-**7a** (275 mg, 0.74 mmol) in TFA/CH_2Cl_2 (each 1 ml) was left at r.t. for 6 h, then evaporated and dried for 1 h at 0.01 Torr. To a cold (5°C) stirred solution of the residue in dry CH_2Cl_2 (10 ml) was added $NaHCO_3$ (1.20 g) and stirring was continued for 45 min at the same temperature. Then Ac_2O (2 ml) was added. After 5 h the solids were filtered off, the filtrate was evaporated at reduced pressure and **14a** (187 mg, 81%) isolated by flash chromatography (CH_2Cl_2/acetone, 4:1, R_f = 0.37) as a colorless, viscous oil.—^{1}H-NMR ($CDCl_3$): δ = 2.04 (s, 3H, $COCH_3$), 3.61 (d, *J* = 11.3 Hz, 6H, $POCH_3$), 4.27 (m_c, 2H, NCH_2), 4.75 (s, 2H, OCH_2), 5.69 (tdd, $J_{1,3} \approx 1.5$, $J_{1,2}$ = 17.2, $J_{1,P}$ = 19.0 Hz, 1H, 1-H), 6.63 (tdd, $J_{2,3}$ = 5.4, $J_{2,1}$ = 17.2, $J_{2,P}$ = 22.2 Hz, 1H, 2-H), 7.24–7.33 (m, $5H_{arom}$).—^{13}C-NMR ($CDCl_3$): δ = 20.14 ($CO\underline{C}H_3$), 48.47

TABLE VIII

N-hydroxy derivatives **10**, **12**, and **13** prepared

	Molecular Formula	Elemental analysis calc. (found) % C	% H	% N	m.p. (°C)	IR (Nujol) ν (cm^{-1})[a]		
10b	$C_{10}H_{21}N_2O_5P$ (280.3)	42.85 (43.25	7.57 7.54	10.00 10.02)	110	3426	3184	1650
10d	$C_{11}H_{23}N_2O_5P$ (294.3)	44.88 (45.06	7.89 7.69	9.52 9.48)	131-33	3445	3204	1657
10e	$C_{16}H_{25}N_2O_5P$ (356.4)	53.92 (53.94	7.08 7.10	7.86 7.84)	143-44	3431 1659	3290	3166
10h	$C_9H_{17}N_2O_5P$ (264.3)	40.90 (41.11	6.50 6.12	10.60 10.50)	152-55	3492	3213	1682
12c[a]	$C_8H_{16}NO_5P$ (237.2)	40.51 (40.98	6.81 6.62	5.91 5.61)	oil	3405	3162	1633
12h	$C_{10}H_{18}NO_5P$ (263.3)	45.62 (45.38	6.91 7.05	5.32 5.13)	116-17	3112	1650	
13b	$C_{11}H_{22}NO_6P$ (295.3)	44.73 (45.08	7.52 7.34	4.74 4.52)	50-52	3188	1704	
13d	$C_{12}H_{24}NO_6P$ (309.4)	46.59 (46.37	7.84 8.01	4.53 4.51)	62-64	3215	1706	
13h	$C_{10}H_{18}NO_6P$ (279.3)	43.00 (42.74	6.51 6.33	5.02 5.12)	120-22	3157	1695	

[a]MS (70 eV): m/z (%) = 237 (14, M^+), 195 (12), 178 (55), 164 (100).

TABLE IX

^{1}H-NMR spectra of N-hydroxy derivatives **10**, **12** and **13** [δ, *J* (Hz)][a]

	1-H	2-H	3-H	OH	$J_{1,P}$	$J_{1,2}$	$J_{1,3}$	$J_{2,P}$	$J_{2,3}$	Substituents
10b	5.88	6.52	4.10	9.45	20.2	17.2	1	22.2	4.9	6.43 (s, NH_2)
10d	5.78	6.57	4.78	9.17	18	17.2	1	22.1	4.9	1.17 (d, 6.9, CH_3CH), 6.43 (s, NH_2)
10e	5.79	7.12	6.02	9.54	19.2	17.2	1.5	22.2	4.9	5.49 (s, NH_2), 7.23 - 7.37 (m, $5H_{arom}$)
10h	-	6.53	4.82	9.35	-	-	-	23.6	2	1.63-1.90 (m, 3H), 1.98 (m_c, 1H), 2.18 (m_c, 2H) [CH_2], 6.58 (s, NH_2)
12c	5.75	6.81	5.25	9.30	19.2	17.7	1.5	22.6	4.9	1.32 (d, 6.9, CH_3CH), 2.15 (s, $COCH_3$)
12h	-	6.68	5.18	9.51	-	-	-	22.6	2	1.66 (m_c, 1H), 1.80 (m_c, 1H), 1.82-1.99 (m, 2H), 2.10 (m_c, 2H) [CH_2], 2.15 (s, $COCH_3$)
13b	5.87	6.71	4.25b	9.20	19.7	17.2	1.5	22.2	4.9	3.69 (s, CO_2CH_3)
13d	5.78	6.86	4.83	8.80	19.2	17.2	1.5	22.6	4.9	1.34 (d, 6.9, CH_3CH), 3.72 (s, CO_2CH_3)
13h	-	6.75	4.73	8.77	-	-	-	23.1	2	1.62 (m_c, 1H), 1.79-1.98 (m, 3H), 2.08 (m_c, 2H) [CH_2], 3.73 (s, CO_2CH_3)

[a]Solvent $CDCl_3$, 25°C: compounds **10e**, **12c,h**, **13b,d,h**; solvent DMSO-d_6, 25°C: compounds **10b,d,h**. [b]$J_{3,P}$ = 3.0 Hz.

($^3J_{PC}$ = 22.8 Hz, CH_2N), 52.23 (J_{PC} = 5.9 Hz, $POCH_3$), 76.83 (OCH_2), 118.05 ($^1J_{PC}$ = 188.6 Hz, PC), 128.52, 129.01 (*o*-, *m*-CH), 128.88 (*p*-CH), 133.99 (*i*-C), 146.60 ($^2J_{PC}$ = 5.5 Hz. C-2), 172.81 (CO).

Dimethyl {3-[N-Acetyl-N-hydroxy)amino]propyl} phosphonate (**15a**)

A. *Hydrogenation with Pd-C/H_2*: A solution of **14a** (54 mg, 0.17 mmol) in dry methanol (2 ml) was

TABLE X

^{13}C-NMR spectra of N-hydroxy derivatives **10**, **12** and **13** [δ,J (Hz)]

	C-1	$^1J_{PC}$	C-2	$^2J_{PC}$	C-3	$^3J_{PC}$	CO	Substituents
10b	119.46	185.5	147.03	4.9	52.17	23.7	161.47	-
10d	118.52	184.4	151.12	4.4	54.49	22.4	161.55	15.77 ($\underline{C}H_3CH$)
10e	120.56	187.9	149.95	6.1	63.05	24.0	161.52	127.94 (*p*-CH), 128.34, 128.93 (*o*-, *m*-CH), 137.22 (*i*-C)
10h	129.03	176.8	144.05	8.4	54.39	18.9	161.65	20.78 (11.4), 23.61 (8.7), 24.05 (s) [CH_2]
12c	115.40	188.7	153.03	s	52.61	23.7	172.20	15.59 ($CH\underline{C}H_3$), 20.57 ($CO\underline{C}H_3$)
12h	129.20	180.0	144.70	9.7	52.56	21.1	172.06	20.90 (11.3), 23.71 (8.3), 24.40 (s) [CH_2], 20.56 ($CO\underline{C}H_3$)
13b	119.72	189.9	146.43	5.5	53.06	25.2	157.88	53.16 ($CO_2\underline{C}H_3$)
13d	118.51	189.5	151.17	5.2	56.16	23.7	157.67	15.67 ($\underline{C}H_3CH$), 53.03 ($CO_2\underline{C}H_3$)
13h	129.36	180.1	144.34	9.8	55.97	20.3	157.63	20.93 (11.3), 23.63 (8.1), 24.24 (1.3) [CH_2], 53.07 ($CO_2\underline{C}H_3$)

[a]Solvent $CDCl_3$, 25°C for compounds **10e**, **12c,h**, **13b,d,h**; solvent DMSO-d_6, 25°C for compounds **10b,d,h**.

stirred over 10% Pd-C (16 mg) under H_2-atmosphere for 1 h at r.t. After filtration, the solvent was removed and **15a** (34 mg, 89%) isolated by flash chromatography (4 g silica gel, EtOAc/MeOH, 9:1, R_f = 0.18) as a colorless viscous oil.

B. *By catalytic transfer hydrogenolysis*: To a solution of **14a** (62 mg, 0.2 mmol) in dry EtOH (2 ml) was added at r.t. with stirring under Ar atmosphere ammonium formate (75 mg, 1.19 mmol) and 10% Pd-C (20 mg). After 50 min **15a** was isolated as given above. Yield 36 mg, 80%. ^{1}H-NMR ($CDCl_3$): δ = 1.78–2.02 (m, 4H, 1-H, 2-H), 2.14 (s, 3H, $COCH_3$), 3.70 (d, J = 10.8 Hz, 6H, $POCH_3$), 3.72 (t, J = 5.9 Hz, 2H, CH_2N), 9.52 (br s, 1H, OH).—^{13}C-NMR ($CDCl_3$): δ = 19.15 ($^2J_{PC}$ = 5.2 Hz, C-2), 20.17 ($CO\underline{C}H_3$), 21.17 ($^1J_{PC}$ = 140.9 Hz, PCH_2), 47.42 ($^3J_{PC}$ = 10.1 Hz, CH_2N), 52.61 (J_{PC} = 6.8 Hz, $POCH_3$), 172.77 (CO).—IR (Si): ν (cm^{-1}) = 3417, 3158, 1633, 1235, 1032 (The CO absorption agrees with the value for the corresponding diisopropylphosphonate,[4] but is different from the values reported for the dimethylester obtained upon esterification of FR 900098 with diazomethane[5]).—MS (70eV): m/z (%) = 225 (5, M^+), 166 (45), 138 (25), 110 (50), 56 (100)

Diisopropyl {3-[(N-hydroxy-N-methoxycarbonyl)amino]butyl} phosphonate (**16d**): A solution of **6d** (195 mg, 0.53 mmol) in dry MeOH (6 ml) was stirred over 10% Pd-C (65 mg) under H_2 atmosphere for 1 h at r.t. After filtration the solvent was concentrated to 1 ml at reduced pressure. To the solution of the crude butylphosphonate (TLC: CH_2Cl_2/EtOAc, 1:9, R_f = 0.38, detection by iodine vapour) was added NH_3/MeOH (sat., 2 ml). Transesterification to **16d** (R_f = 0.21) was complete after 20 min. The solvent was removed and **16d** (151 mg, 92%) isolated by filtration over silica gel (CH_2Cl_2/EtOAc, 1:9) as a colorless, viscous oil.—^{1}H-NMR ($CDCl_3$): δ = 1.16 (d, J = 6.4 Hz, 3H, $C\underline{H}_3CH$), 1.25, 1.27, 1.28, 1.29 [4d, J = 6.9, 5.9, 6.9, and 6.9 Hz, each 3H, $POCH(C\underline{H}_3)_2$], 1.59–1.97 (m, 4H, 1-H, 2-H), 3.72 (s, 3H, OCH_3), 4.14 (m_c, 1H, CHN), 4.62 (m_c, 2H, POCH), 8.70 (br s, 1H, OH).—^{13}C-NMR ($CDCl_3$): δ = 17.02 ($\underline{C}H_3CH$), 23.39 ($^1J_{PC}$ = 142.6 Hz, PCH_2), 23.84, 23.90, 23.94, 23.95 [J_{PC} = 4.6, 4.3, 4.5, and 4.8 Hz, $POCH(\underline{C}H_3)_2$], 25.23 ($^2J_{PC}$ = 5.1 Hz, C-2), 52.87 (OCH_3), 55.19 ($^3J_{PC}$ = 9.0 Hz, CHN), 70.46, 70.75 ($^2J_{PC}$ = 6.9, 6.7 Hz, POCH), 158.16 (CO).—IR (Si) ν (cm^{-1}) = 3188 (OH), 1694 (CO).—MS (70eV): m/z (%) = 311 (4, M^+), 227 (15), 137 (28), 135 (100).

[*N-(3-Diisopropoxyphosphonylpropyl)-N-hydroxy*]*urea* (**17b**): **5b** (437 mg, 1.0 mmol) was prepared and hydrogenated as given in Reference 14. The catalyst was filtered off, the filtrate was evaporated at reduced pressure, the residue dried by coevaporation with toluene and at 0.01 Torr, then dissolved in CH_2Cl_2/TFA (each 2 ml), and left for 6 h at r.t. After evaporation, the trifluoroacetate was dried at 0.01 Torr, and then dissolved in THF/H_2O (each 4 ml). To the solution was added KOCN (100 mg, 1.24 mmol) at r.t. Stirring was continued for 16 h, then the solvents were evaporated and **17b** (129 mg, 45%) isolated by flash chromatography (14 g silica gel, CH_2Cl_2/MeOH 15:1, R_f = 0.36) as colorless crystals, m.p. 115–117°C (EtOAc).—^{1}H-NMR ($CDCl_3$): δ = 1.29 [d, J = 6.4 Hz, 12H, $POCH(C\underline{H}_3)_2$], 1.75–1.97 (m, 4H, 1-H, 2-H), 3.58 (t, J = 5.9 Hz, 2H, NCH_2), 4.62 (m_c, 2H, POCH), 5.38 (br s, 2H, NH_2), 9.74 (br s, 1H, OH).—^{13}C-NMR ($CDCl_3$): δ = 19.66 ($^2J_{PC}$ = 5.4 Hz, C-2), 23.59 ($^1J_{PC}$ = 142.2 Hz, PCH_2), 23.91, 23.95 [J_{PC} = 4.6 and 3.8 Hz, $POCH(\underline{C}H_3)_2$], 49.43 ($^3J_{PC}$ = 8.7 Hz, CH_2N), 70.75 ($^2J_{PC}$ = 6.9 Hz,

POCH), 161.58 (CO).—IR (Nujol): ν (cm^{-1}) = 3423, 3200, 1644, 1228.

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