Pergamon

Tetrahedron, Vol. 53, No. 38, pp. 12961-12978, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00814-4

Diastereo- and Enantioselective Synthesis of 2,3- and 1,2-Disubstituted 4-Oxophosphonates via Asymmetric Michael Addition

Dieter Enders*, Heiner Wahl and Kyriakos Papadopoulos

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule,

Professor-Pirlet-Straße 1, D-52074 Aachen, Germany

Abstract: Asymmetric Michael addition of lithiated SAMP hydrazones (*S*)-**2** to a variety of alkenylphosphonates (*E*)-**3** followed by oxidative cleavage of the 1,4-adducts **4** afforded 2,3-disubstituted 4-oxophosphonates **5** with good to very good yields (58-80%), low to moderate diastereomeric (*de* = 6-74%) and excellent enantiomeric excesses (*ee* = >93%). Pure *anti*-diastereomers (*ee* = >93%) of **5** were obtained by separation of the stereoisomers by HPLC. In addition, the lithiated SAMP hydrazone (*S*)-**2a** was added to alkenylphosphonates (*E*)-**3**, and the lithio phosphonate anions were trapped with alkyl halides or sulfates, yielding 1,2-disubstituted 4-oxophosphonates **8** with moderate to good yields (38-69%), low to good diastereomeric (*de* = 10-77%) and high enantiomeric excesses (*ee* = >90%) after oxidative cleavage.

INTRODUCTION

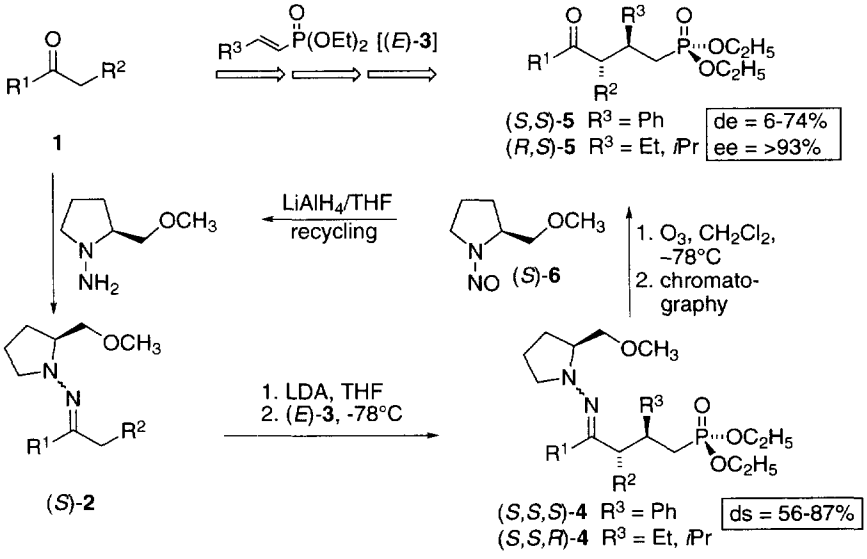
The Michael addition of nucleophiles to alkenylphosphonates is a well established method in organic synthesis for the preparation of substituted phosphonates[1]. However, only a few applications of this methodology in asymmetric synthesis have been published[1,2,3]. The first enantioselective synthesis of isosteres of phosphothreonine was accomplished via conjugate addition of the lithium salt of Schöllkopf's bislactim ether to (*E*)-vinylphosphonates[3]. Recently, we reported on an efficient enantioselective synthesis of 2-substituted 4-oxophosphonates using the SAMP/RAMP methodology in Michael addition reactions[1]. We now wish to present some useful extensions of this method, leading to 2,3- and 1,2-disubstituted 4-oxophosphonates via diastereo- and enantioselective 1,4 additions to (*E*)-alkenylphosphonates[4,5].

RESULTS AND DISCUSSION

Firstly, a variety of aryl ethyl ketones and diethyl ketone **1** were transformed to the corresponding SAMP hydrazones (*S*)-**2**, following standard literature procedures[6]. Then, the SAMP hydrazones (*S*)-**2** were metallated with lithium diisopropylamide in THF at –78°C[6]. The Michael additions were carried out by addition of the (*E*)-alkenylphosphonates (*E*)-**3** (R^3 = Et, *i*Pr, Ph) to the aza enolates. The reaction was completed within 3-5h as was indicated by tlc control. After aqueous workup and purification by column chroma-

tography, the Michael adducts **4** were obtained as yellow oils in 64-84% yield, refering to the carbonyl compounds **1** (Scheme 1). The hydrazones were formed with moderate to good diastereoselectivities (56-87%, Table 1) which were determined by ^{13}C NMR spectroscopy as well as analytical HPLC. A Michael Michael tandem process, the side reaction detected during the synthesis of the 2-substituted phosphonates[1], was not observed in this reaction sequence, even when more reactive Michael acceptors (R^3 = Ph, Et) were utilized. This may be due to the steric hindrance caused by the additional substituent at C-2' (***C***HR^2), reducing the reactivity of the intermediate lithio phosphonate anion for a further 1,4-addition to the phosphonate Michael acceptors.

Spectra and chromatograms showed complex mixtures of stereoisomers [(*E*), (*Z*), *syn*, *anti*, *de*(*syn*), *de*(*anti*)]. Upon heating of compounds **4a-d** (R^1 = aryl) to about 100°C, isomerization of the kinetically formed (*E*)-isomers to the more stable (*Z*)-configurated compounds occurred as was evident from the ^{13}C NMR spectra. Generally, a significant high field shift of the ***C***=N carbon of the aryl substituted hydrazones **4a-d** was observed when converting the (*E*)- to the favoured (*Z*)-isomers. For example, the (*Z*)-isomers gave resonances at about 155 ppm whereas the signals of the (*E*)-isomers were observed at 169 ppm.



Scheme 1. Michael Addition of SAMP Hydrazones to Alkenylphosphonates.

Irrespective of the (*E*)/(*Z*) isomerism it turned out that only two diastereomers were detectable by ^{13}C NMR or HPLC in compounds **4a-d**. The stereocenter at C-2' was formed with uniform configuration as was proven by the following reaction sequence: Hydrazone **4a** was treated with lithium diisopropylamide in THF at 0°C for 4h. Then, after hydrolysis and isolation, four diastereomers much predominantly in (*Z*)-configuration were detected by ^{13}C NMR. This result can be simply rationalized by deprotonation and unselective reprotonation of the stereocenter at C-2', bearing an acidic hydrogen atom. Nevertheless, only two of these four possible diastereomers were detected in our original sample obtained by the stereoselective Michael addition of the

metallated hydrazones to the alkenylphosphonates, reflecting a *syn/anti* isomer ratio with the *anti* isomer predominantly formed.

Table 1. Diastereoselective Synthesis of Hydrazones **4**.

4	R^1	R^2	R^3	yield[a] [%]	*ds*[b,c] [%]	Config.[d]
a	Ph	Me	Et	71 (64)	56	(*S,S,R*):(*S,S,S*)
b	Ph	Me	*i*Pr	92 (84)	68 (64)	(*S,S,R*):(*S,S,S*)
c	Ph	Me	Ph	93 (84)	80 (81)	(*S,S,S*):(*S,S,R*)
d	2-Naph	Me	Ph	93 (84)	87 (85)	(*S,S,S*):(*S,S,R*)
e	Et	Me	Ph	82 (74)	[e]	(*S,S,S*):(*S,S,R*)

[a] Values in brackets refer to the chemical yields, starting from **1** (2 steps). - [b] Determined by ^{13}C NMR spectroscopy. Values in brackets were determined by analytical HPLC. - [c] No diastereomers with (*R*) configuration at stereocenter C-2' were determined by ^{13}C NMR spectroscopy or analytical HPLC. - [d] The first letter refers to the configuration of the auxiliary. The configurations were deduced from previous results and the relative configuration of **5**. - [e] Ratio was not determined.

On the basis of many previous results on conjugate additions[7] and electrophilic substitutions[8] via SAMP/RAMP hydrazones, we assumed that the reaction had taken place following the established mechanism for Michael additions of SAMP/RAMP hydrazones. Therefore, we postulate the stereocenter at C-2' to be formed with the absolute configuration (*S*).

Cleavage of pure and/or crude adduct hydrazones **4** was readily achieved by ozonolysis at –78°C in dichloromethane, leading to 2,3-disubstituted 4-oxophosphonates **5** that were separated from nitrosamine (*S*)-**6** by column chromatography.

Table 2. 4-Oxophosphonates **5** by Ozonolysis of SAMP Hydrazones **4**.

5	R^1	R^2	R^3	yield[a] [%]	*de*[b] [%]	*ee*[c] [%]	confg.[d]
a	Ph	Me	Et	90	9 (6)	>93	(*R,S*)
b	Ph	Me	*i*Pr	74[e]	34 (33)	>93	(*R,S*)
c	Ph	Me	Ph	95	58 (57)	>93	(*S,S*)
d	2-Naph	Me	Ph	76	74 (73)	>93	(*S,S*)
e	Et	Me	Ph	95	57	-	(*S,S*)

[a] Yield based on **4** (1 step). - [b] Determined by ^{13}C NMR spectroscopy. Values in brackets were determined by analytical HPLC. - [c] Deduced from the diastereoselectivities of compounds **4**. - [d] Major isomer with *anti* configuration. - [e] Yield based on **1** (3 steps).

The phosphonates **5** (Table 2) were obtained in good to excellent overall yields of 58-80% (3 steps), 6-74% diastereomeric excesses and enantiomeric excesses of >93%[9]. The nitrosamine (*S*)-**6** can be recovered and reduced with $LiAlH_4$ in THF, allowing a recycling of the chiral auxiliary SAMP[6b]. The *de* values of compounds **5a-d** correspond to the *ds* values of hydrazones **4a-d** (Table 1). This fact proofs that no racemization occurred during ozonolysis or product isolation, and thus the deduction of the *ee* values of **5** from the *ds* values of **4** is correct. This is supported by earlier results of our group[7b] where ketones bearing alkyl substituted stereogenic centers in α position to carbonyl group did not racemize during ozonolysis or simple column chromatography on silica gel. Pure *anti* and *syn* diastereomers (*de* = >95%; *ee* = >93%) were obtained by separation by preparative HPLC on silica gel columns (Table 3).

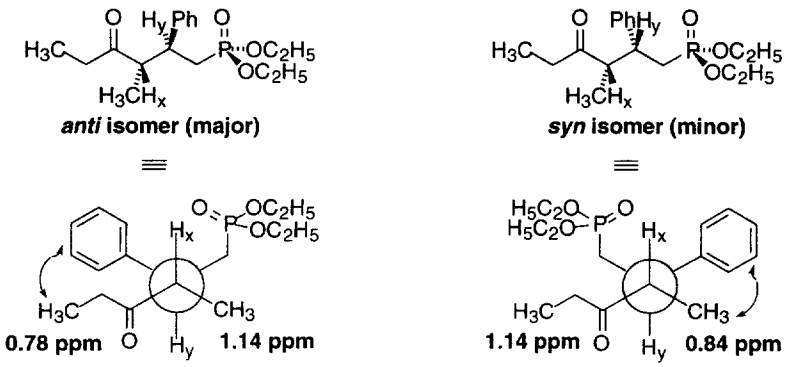
Table 3. Pure Diastereomers of **5** from Separation by Preparative HPLC.

5	R^1	R^2	R^3	$[\alpha]_D^{25}$ (c, $CHCl_3$)	*de*[b] [%]	*ee*[c] [%]	confg.[a]	$[\alpha]_D^{25}$ (c, $CHCl_3$)	*de*[b] [%]	*ee*[c] [%]	confg.[d]
a	Ph	Me	Et	+36.8 (0.8)	>95[e]	>93	(*R*,*S*)	+32.5 (1.1)	>95[e]	>93	(*S*,*S*)
b	Ph	Me	*i*Pr	+33.7 (1.0)	>95[e]	>93	(*R*,*S*)	+30.9 (1.0)	>95[e]	>93	(*S*,*S*)
c	Ph	Me	Ph	+20.4 (1.0)	>95	>93	(*S*,*S*)	+35.0 (0.7)	>95	>93	(*R*,*S*)
d	2-Naph	Me	Ph	-42.0 (0.9)	>95	>93	(*S*,*S*)	+39.0 (0.3)	>95	>93	(*R*,*S*)

[a] *anti* isomer. - [b] Determined by analytical HPLC. - [c] Deduced from the diastereomeric purity of compounds **4**. - [d] *syn* isomer. - [e] Confirmed by ^{13}C NMR spectroscopy.

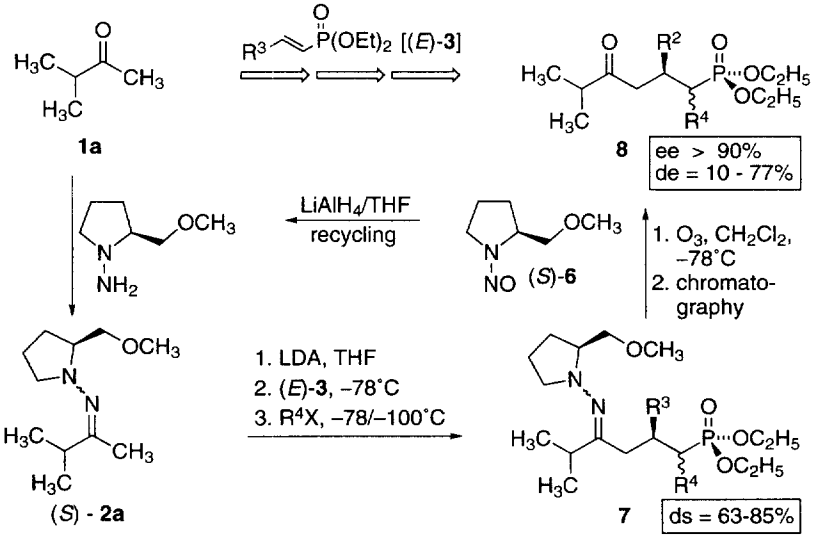
The relative configuration of the title compounds **5** was deduced from careful studies of ^1H NMR spectra on compound **5e** and *rac*-**5e**. In the case of the major isomer, the ^1H NMR resonances of the hydrogen H_x appear as a doublet quartet, revealing coupling constants of 8.6 (J_{H_x,H_y}) and 6.9 Hz (J_{H_x,CH_3}) (9.6 and 6.9 Hz for the minor isomer), respectively. The vicinal coupling constants of about 9 Hz indicate a preferred antiperiplanar conformation of H_x and H_y in the major as well as the minor isomer. Assuming this conformation, a high field shift of the methyl resonance of $\boldsymbol{H_3C}CH_2CO$ was expected in the case of the *anti* configuration due to anisotropic effects of the phenyl substituent. In the *syn* isomer the methyl signal of $CH_x\boldsymbol{CH_3}$ should be shifted upfield.

As is depicted in Scheme 2, both predicted effects a) the high field shift of $\boldsymbol{H_3C}CH_2CO$ group in the major isomer and b) the high field shift of the $CH_x\boldsymbol{CH_3}$ group in the minor isomer were observed. Similar resonance shifts were observed in the ^1H NMR spectra for example of compounds **5c** and **5d**. Thus, we assumed that the phosphonates were generally formed with *anti* configuration. In contrast to this result, the racemic phosphonates *rac*-**5**, prepared by analogous 1,4-additions (Scheme 1) using achiral dimethylhydrazone homocuprates[10], were predominantly formed with *syn* configuration.



Scheme 2. Deduction of Relative Configuration from NMR Experiments.

We then directed out attention to further explore this methodology towards the synthesis of 1,2-disubstituted 4-oxophosphonates. In Scheme 3, a simple and efficient diastereo- and enantioselective synthesis of this class of compounds **8** is presented. 3-Methylbutanone **1a** was converted to the corresponding SAMP hydrazone (*S*)-**2a** which was metallated and then added to various alkenylphosphonates (*E*)-**3** following the standard protocol. The intermediate P=O stabilized adduct anions[11] were trapped with alkyl bromides, iodides or sulfates (Table 4, Table 5) at –78 or –100°C, giving the tandem adduct hydrazones **7a,b**.



Scheme 3. Michael/α-Alkylation Tandem Reactions of SAMP Hydrazones.

After workup and isolation by column chromatography the tandem adduct hydrazones **7a,b** were obtained in good yields (62-69%, 2 steps, Table 4) and with moderate to good diastereoselectivities (63-85%) which were determined by ^{13}C NMR spectroscopy.

As reported previously[1,7] the stereogenic center at C-3' (*C*HR^3) is predominantly formed with (*S*) configuration (*ee* = 92->95%) via the described 1,4-addition. Therefore, the diastereoselectivities of compounds **7**, given in Table 5, directly reflect the stereoselectivity of the tandem alkylation step.

Table 4. Diastereoselective Synthesis of Hydrazones **7**.

7	R^3	R^4	R^4X	yield[a] [%]	*ds*[b,c] [%]
a	*i*Pr	Me	$(H_3CO)_2SO_2$	62	85
b	*i*Pr	Bn	BnBr	69	63

[a] Yield based on **1a** (2 steps). - [b] Relative configuration of the major diastereomer unknown; 3' stereocenter with uniform (*S*) configuration.[7] - [c] Determined by ^{13}C NMR spectroscopy.

The pure or crude 1,2-disubstituted hydrazonephosphonates **7** were cleaved by ozonolysis, furnishing the title compounds **8** and nitrosamine (*S*)-**6** which were separated and isolated by column chromatography. The 1,2-disubstituted 4-oxophosphonates **8** were isolated with moderate to good overall yields (38-69%, 3 steps, Table 5), diastereomeric excesses of 10-77% and enantiomeric excesses of >90%. Whereas the absolute configuration of stereocenter C-2 (*C*HR^2) is (*S*), unfortunately, we were not able to determine the relative configuration of compounds **8**.

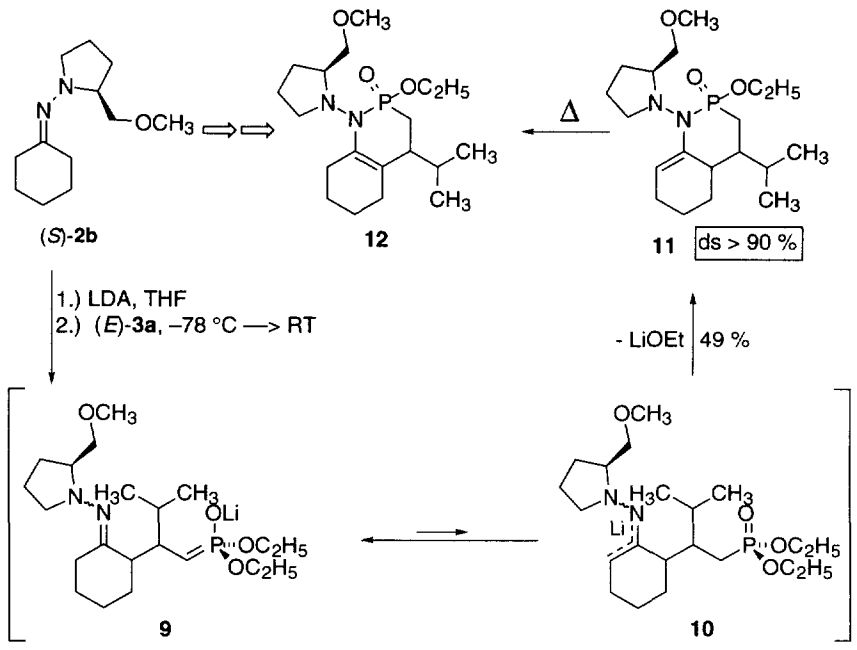
Table 5. Diastereoselective Synthesis of 4-Oxophosphonates **8**.

8	R^3	R^4	R^4X	yield[a] [%]	$[\alpha]_D^{25}$ (neat)	*de*[b,c] [%]	*ee*[d] [%]
a	*i*Pr	Me	$(H_3CO)_2SO_2$	65	-[e]	66	>95
a	*i*Pr	Me	H_3CI	62	+4.9	53	>95
b	*t*Bu	Me	H_3CI	69	+3.9	77[f] (77)	>95
c	Ph	Me	H_3CI	38	0.0	50 (51)	92
d	*i*Pr	Et	EtI	56	-[e]	-[e] (10)	>95
e	*i*Pr	Bn	BnBr	83[g]	-10.2	30[h]	>95

[a] Overall yield starting from **1a** (3 steps). - [b] Determined by ^{13}C NMR spectroscopy. Yields in brackets were determined by GC. - [c] Relative configuration of the major diastereomer unknown. - [d] Stereocenter at C-2 with (*S*) configuration[7]. - [e] Not determined. - [f] Confirmed by ^{31}P NMR spectroscopy. - [g] Yield starting from **7b** (1step). - [h] Confirmed by analytical HPLC.

Finally, we wish to report on some unexpected cyclization products obtained by reaction of cyclohexanone SAMP hydrazone (*S*)-**2b** and [(*E*)-3-methylbuten-1-yl]phosphonate (*E*)-**3a**. In our attempt to extend this method to cyclic hydrazones, (*S*)-**2b** and the Michael acceptor were combined under the usual reaction condi-

tions. However, we were not able to isolate the expected Michael adduct, instead, the cyclization product **11** was isolated in 49% yield. Obviously, an intramolecular proton transfer among the phosphonate anion **9** and the lithiated enhydrazine **10** is possible, and the lithio enhydrazine **10** underwent spontaneous cyclization, forming the bicyclic compound **11** (Scheme 4).



Scheme 4. Cyclization Reaction of SAMP Hydrazones with Phosphonates.

After column chromatography **11** was isolated in 49% yield. Although **11** bears 3 stereogenic centers, only one stereoisomer was detectable by ^{13}C NMR and analytical HPLC. Probably only one of the diastereomeric anions from the Michael addition formed a cyclic octahydro-benzazaphosphinin-2-one structure with a sufficient stability. Compound **11** was converted by heating to the more stable enehydrazine **12**, that was purified by column chromatography.

CONCLUSION

In summary, the diastereo- and enantioselective Michael addition of ethyl ketones to alkenylphosphonates via lithiated SAMP/RAMP hydrazones offers an efficient entry to a variety of 2,3-disubstituted 4-oxophosphonates. Pure *syn* and *anti* diastereomers of high enantiomeric purity may be isolated after separation by HPLC. In addition, 1,2-disubstituted 4-oxophosphonates can be obtained in good overall yields, high enantiomeric and moderate to good diastereomeric excesses by Michael/α-alkylation tandem reactions employing alkyl halides or sulfates. Thus the scope of Michael reactions via SAMP/RAMP hydrazones is further

extended[1,7]. Needless to mention by utilising RAMP instead of SAMP the optical antipodes of the title compounds are directely accessible, too.

EXPERIMENTAL SECTION

General. All reactions were carried out using standard Schlenk techniques. Solvents were dried and purified by conventional methods prior to use. Tetrahydrofuran was freshly distilled from sodium under argon. Reagents were purchased from common commercial suppliers and were used from freshly opened containers unless otherwise stated. The (*E*)-alkenylphosphonates[12,13] (*E*)-**3** and SAMP hydrazones (*S*)-**2** were synthesized according to literature procedures.[14]

Apparatus. Optical rotations: Perkin-Elmer P 241 polarimeter; solvents of Merck UVASOL quality. - IR spectra: Beckman Acculab 4, Perkin-Elmer 1420 or Perkin-Elmer FT 1750. - ^{1}H NMR spectra (90 MHz or 300 MHz), ^{31}P NMR spectra (121 MHz) and ^{13}C NMR spectra (75 MHz): Varian EM 390 or Varian VXR 300 (δ in ppm, solvent: $CDCl_3$, TMS as internal and H_3PO_4 as external standard, respectively). - Mass spectra: Finnigan MAT 212 (EI 70 eV). - Microanalyses: Heraeus Mikro U/D or Heraeus CHN-O-RAPID. - Ozonolyses: Fischer ozone generator type 502. - HPLC: Du Pont HPLC 830, UV detection, two coupled Zorbax-Sil columns (25 cm × 2.5 cm, 7 µm silica); Waters Instrument 590, UV detection, 5 µm silica phase; *n*-hexane:isopropanol 96:4.

(S)-(+)-2-Methoxymethyl-1-[1'-(2''-naphthyl)propylideneamino]pyrrolidine: A Schlenk flask was charged with 5.6 g (20 mmol) 2-naphthylmethylketone SAMP hydrazone and THF (25 ml). The flask was cooled to 0°C, and lithium diisopropylamide (22 mmol), prepared from *n*-BuLi (1.5 M in *n*-hexane) and diisopropylamine in THF (30 ml) at 0°C, was added dropwise and the mixture was stirred at 0°C. After 4 h the reaction mixture was cooled to –78°C and 1.3 ml (21 mmol) methyliodide were added dropwise. After 1 h the mixture was allowed to warm to room temperature and H_2O (20 ml) was added. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 ml). The combined extracts were dried ($NaSO_4$) and concentrated under reduced pressure. The hydrazone was purified by column chromatography (silica gel; *n*-hexane:ether 1:1), yielding 5.6 g hydrazone (95%) as a yellow, viscous oil. - $[\alpha]_D^{25}$ = +740.6 (0.98, $CHCl_3$). - IR (film): $\tilde{\nu}$ = 3050 cm^{-1}, 2965, 2930, 2875, 1600, 1500, 1460, 1345, 1300, 1275, 1195, 1130, 1055, 1020, 970, 935, 890, 860, 825, 750. - ^{1}H NMR: δ = 1.13 (t, 3H, CH_2CH_3), 1.67-2.14 (m, 4H, CH_2CH_2), 2.65 (q, 1H, NC*H*H), 2.91 (q, 2H, CH_2CH_3), 3.28-3.58 (m, 4H, $NCHCH_2OCH_3$, NCH*H*), 3.34 (s, 3H, OCH_3), 7.30-7.50 (m, 2H, arom.), 7.72-7.85 (m, 3H, arom.), 7.93-8.50 (m, 2H, arom.). - ^{13}C NMR: δ = 12.0 (CH_3), 22.4, 22.7, 26.8 (CH_2CH_3, CH_2CH_2), 55.7 (CH_2N), 59.1 (OCH_3), 66.9 (NCH), 75.7 (CH_2OCH_3), 124.7, 125.9, 126.0, 126.1, 127.5, 127.7, 128.4 (CH arom.), 133.2, 133.6, 135.4 (C arom.), 164.4 (C=N). - MS (70eV); *m/z* (%) = 296 (17) [M^+], 251 (75) [M^+-CH_2OCH_3], 182 (100), 127 (54) [$H_7C_{10}^+$]. - $C_{19}H_{24}N_2O$ (296.5): Calcd. C 76.97, H 8.18, N 9.45; found C 76.94, H 8.13, N 9.55.

General procedure 1 for Michael additions to α,β-unsaturated phosphonates:

A solution of *n*BuLi (1.1 equiv., 1.6 M in *n*-hexane) was added dropwise to a solution of diisopropylamine (1.1 equiv.) in THF (30 ml/10 mmol) at 0°C under an atmosphere of argon. After 15 min the LDA (1.1 equiv.) solution had been generated and SAMP hydrazones (*S*)-**2** (1.0 equiv.), dissolved in THF (20 ml/10 mmol), were added dropwise and the reaction mixture was stirred at 0°C[6]. After 3-5 h the reaction mixture was cooled to –78°C and the (*E*)-alkenylphosphonate (*E*)-**3** (1.0 equiv.) was slowly added. Stirring was continued at –78°C for 3-5 h, and the reaction was monitored by tlc.

Synthesis of hydrazones **4**: After completion of the Michael addition the reaction mixture was added to a saturated ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 ml). The combined extracts were washed with water (50 ml), dried ($NaSO_4$) and concentrated under reduced pressure, yielding the crude Michael adducts as yellow to brown yellow, viscous oils which were purified by column chromatography (silica gel; acetonitrile/ethyl acetate 1:1) or cleaved without purification by ozonolysis.

Synthesis of Michael tandem products **7**: The anions, generated by the Michael addition, were trapped by dropwise addition of an electrophile (1.00-1.05 equiv.; alkyl halide, dimethyl sulfate) at –78°C or –100°C (liquid N_2/pentane). After 1h the mixture was allowed to warm to room temperature overnight, H_2O (20 ml) was added and the tandem adducts were purified as described for the hydrazones **4**.

(2S,2'S,3'R/S)-(+)-1-[3'-[(Diethoxyphosphoryl)methyl]-2'-methyl-1'-phenylpentylideneamino]-2-methoxymethylpyrrolidine [(*S,S,R/S*)-**4a**]: 2.46 g (10 mmol) Propiophenone SAMP hydrazone and 1.92 g (10 mmol) diethyl (*E*)-(buten-1-yl)phosphonate were reacted according to general procedure 1, yielding 3.10 g of (*S,S,R/S*)-**4a** (71%) as clear yellow oil after column chromatography. - $[\alpha]_D^{25}$ = +309.2 (1.01, $CHCl_3$)[15]. - *syn*:*anti* = 44:56. - *de* (*anti*) = >95%[16]. - IR (film): $\tilde{\nu}$ = 2980 cm^{-1}, 1245 (P=O), 1035, 965, 700. - ^1H NMR [(*S,S,R*)-**4a**, (*S,S,S*)-**4a**]: δ = 0.76, 0.78 (2t, 6H, $CHCH_2CH_3$), 1.03, 1.11 (2d, 6H, $CHCH_3$), 1.19, 1.24, 1.24 (4t, 12H, OCH_2CH_3), 1.35-3.70 [m, 28H, CH_2CH_2, NCH_2, $NCHCH_2OCH_3$, $CH(CH_2CH_3)CH_2P$], 2.96 [dq, 1H, $CH(CH_3)$], 3.08 [ddq, 1H, $CH(CH_3)$], 3.39, 3.40 (2s, 6H, OCH_3), 3.80-4.15 (m, 8H, OCH_2CH_3), 7.16-7.38 (m, 10H, arom.). - ^{13}C NMR: δ = 11.2, 11.5, 11.6, 13.5 (CH_3), 16.4 (2d, OCH_2CH_3), 22.7, 25.1 (2d, CH_2CH_3), 22.9, 23.0, 26.8 (CH_2CH_2), 25.2, 27.3 (2d, CH_2P), 36.3, 36.9 (2d, $CHCH_2P$), 41.3, 43.4 (2d, $CHCH_3$), 54.46, 54.52 (CH_2N), 59.1, 59.2 (OCH_3), 61.1 (2d, OCH_2CH_3), 66.5, 66.6 (NCH), 76.2 (CH_2OCH_3), 127.0-128.5 (m, CH arom.), 139.2, 139.5 (C arom.), 155.2, 156.1 (C=N). - MS (70eV); *m/z* (%) = 438 (48) [M^+], 393 (89) [$M^+-CH_2OCH_3$], 324 (100), 55 (41). - $C_{23}H_{39}N_2O_4P$ (438.6): calcd. C 62.98, H 8.98, N 6.39; found C 63.10, H 8.82, N 6.47.

(2S,2'S,3'R/S)-(+)-1-[3'-[(Diethoxyphosphoryl)methyl]-2',4'-dimethyl-1'-phenylpentylideneamino]-2-methoxymethylpyrrolidine [(*S,S,R/S*)-**4b**]: 1.23 g (5 mmol) Propiophenone SAMP hydrazone and 1.03 g (5 mmol) diethyl [(*E*)-3-methylbuten-1-yl]phosphonate were reacted according to general procedure 1, yielding 2.10 g of (*S,S,R/S*)-**4b** (93%) as yellow oil after column chromatography. - $[\alpha]_D^{25}$ = +316.8 (1.33, $CHCl_3$)[15]. -

syn:*anti* = 32:68. - *de* (*anti*) = >95%[16]. - IR (film): $\tilde{\nu}$ = 3070 cm^{-1}, 2990, 1250 (P=O), 1040, 965, 705. - ^1H NMR [(*S,S,R*)-**4b**]: δ = 0.70-0.93 [m, 6H, $CH(CH_3)_2$], 1.10-1.33 (m, 9H, OCH_2CH_3, $CHCH_3$), 1.40-4.15 [m, 18H, CH_2CH_2, NCH_2, $NCHCH_2OCH_3$, $(H_3C)_2CHCHCH_2P$, CNCH, OCH_2CH_3], 3.40 (s, 3H, OCH_3), 7.17-7.42 (m, 5H, arom.). - ^{13}C NMR: δ = 14.0 ($CHCH_3$), 16.4 (d, OCH_2CH_3), 19.3, 22.6 [$CH(CH_3)_2$], 23.0, 26.8 (CH_2CH_2), 24.0 (d, CH_2P), 27.5 [d, $CH(CH_3)_2$], 39.7 (d, $CHCH_2P$), 43.9 (d, $CHCH_3$), 54.4 (CH_2N), 59.2 (OCH_3), 61.1 (2d, OCH_2CH_3), 66.5 (NCH), 76.2 (CH_2OCH_3), 127.3, 127.9, 128.2 (CH arom.), 139.2 (C arom.), 156.2 (C=N); (*S,S,S*)-**4b** (partial) δ = 15.4 ($CHCH_3$), 19.5, 19.9 [$CH(CH_3)_2$], 23.0, 26.9 (CH_2CH_2), 23.2 (d, CH_2P), 30.0 [d, $CH(CH_3)_2$], 40.3 (d, $CHCH_2P$), 41.9 (d, $CHCH_3$), 54.6 (CH_2N), 66.6 (NCH), 76.2 (CH_2OCH_3). - MS (70eV); *m/z* (%) = 452 (61) [M^+], 409 (28) [M^+–$CH(CH_3)_2$], 407 (62) [M^+–CH_2OCH_3], 338 (100). - $C_{24}H_{41}N_2O_4P$ (452.6): calcd. C 63.68, H 9.15, N 6.19; found C 63.62, H 9.09, N 6.30.

(2S,2'S,3'S/R)-(+)-1-[4'-(Diethoxyphosphoryl)-2'-methyl-1',3'-diphenylbutylideneamino]-2-methoxymethylpyrrolidine [(*S,S,S*)-**4c**]: 2.46 g (10 mmol) Propiophenone SAMP hydrazone and 2.40 g (10 mmol) diethyl [(*E*)-2-phenylethenyl]phosphonate were reacted according to general procedure 1, yielding 4.50 g of (*S,S,S/R*)-**4c** (93%) as a yellow, viscous oil after column chromatography. - $[\alpha]_D^{25}$ = +284.8 (1.00, $CHCl_3$)[15]. - *syn*:*anti* = 20:80. - *de* (*anti*) = >95%[16]. - IR (film): $\tilde{\nu}$ = 3060 cm^{-1}, 3030, 2980, 2930, 2880, 1250 (P=O), 1100, 1035, 965, 700. - ^1H NMR [(*S,S,S*)-**4c**]: δ = 0.90-1.14 (m, 6H, CH_2CH_3), 1.17 (d, 3H, $CHCH_3$), 1.40-3.90 (m, 17H, CH_2CH_2, NCH_2, $NCHCH_2OCH_3$, $CHCHCH_2P$, CH_2CH_3), 3.41 (s, 3H, OCH_3), 7.05-7.40 (m, 10H, arom.); (*S,S,R*)-**4c** (partial) δ = 0.82 (d, 3H, $CHCH_3$), 3.38 (s, 3H, OCH_3). - ^{13}C NMR: δ = 15.1 ($CHCH_3$), 16.1 (2d, OCH_2CH_3), 23.1, 26.8 (CH_2CH_2), 26.1 (d, CH_2P), 43.0 (d, $CHCH_2P$), 48.7 (d, $CHCH_3$), 54.7 (CH_2N), 59.2 (OCH_3), 61.0 (2d, OCH_2CH_3), 66.5 (NCH), 76.1 (CH_2OCH_3), 126.0-129.0 (m, CH arom.), 139.8, 143.0 (C arom.), 154.1 (C=N); (*S,S,R*)-**4c** (partial) δ = 18.5 ($CHCH_3$), 30.9 (d, CH_2P), 43.9 (d, $CHCH_2P$), 49.0 (d, $CHCH_3$), 54.9 (CH_2N), 59.1 (OCH_3), 66.5 (NCH), 76.0 (CH_2OCH_3), 139.3 (C arom.), 142.5 (C=N). - MS (70eV); *m/z* (%) = 486 (59) [M^+], 441 (97) [M^+–CH_2OCH_3], 372 (92), 245 (100), 132 (86), 131 (57). - $C_{27}H_{39}N_2O_4P$ (486.7): calcd. C 66.63 H, 8.09, N 5.76; found C 67.20, H 7.99, N 6.16.

(2S,2'S,3'S/R)-(+)-1-[4'-(Diethoxyphosphoryl)-2'-methyl-1''-(2''-naphthyl)-3'-phenylbutylideneamino]-2-methoxymethylpyrrolidine [(*S,S,S/R*)-**4d**]: 1.48 g (5 mmol) 2-Naphthylethylketone SAMP hydrazone (*S*)-**3a** and 1.20 g (5 mmol) diethyl [(*E*)-2-phenylethenyl]phosphonate were reacted according to general procedure 1, yielding 2.50 g of (*S,S,S/R*)-**4d** (93%) as brown yellow, viscous oil after column chromatography. - *syn*:*anti* = 13:87. - *de* (*anti*) = >95%[16]. $[\alpha]_D^{25}$ = +300.5 (0.87, $CHCl_3$)[15]. - IR ($CHCl_3$): $\tilde{\nu}$ = 3060 cm^{-1}, 3030, 2980, 2935, 2880, 1250 (P=O), 1100, 1030, 965. - ^1H NMR [(*S,S,S*)-**4d**]: δ = 0.99, 1.01 (2t, 6H, CH_2CH_3), 1.25 (d, 3H, $CHCH_3$), 1.40-4.20 (m, 15H, CH_2CH_2, NCH_2, $NCHCH_2OCH_3$, $CHCHCH_2P$, CH_2CH_3), 3.44 (s, 3H, OCH_3), 7.00-7.90 (m, 12H, arom.); (*S,S,R*)-**4d** (partial) δ = 0.90 (d, 3H, $CHCH_3$), 3.40 (s, 3H, OCH_3). - ^{13}C NMR: δ = 15.6 ($CHCH_3$), 16.1, 16.2 (2d, OCH_2CH_3), 23.1, 26.9 (CH_2CH_2), 26.4 (d, CH_2P), 43.4 (d, CHPh), 48.9 (d, $CHCH_3$), 55.0 (CH_2N), 59.2 (OCH_3), 61.0, 61.0 (2d, OCH_2CH_3), 66.6 (NCH), 76.1 (CH_2OCH_3), 125.5-144.0 (C/CH arom.), 153.9 (C=N); (*S,S,S*)-**4d** (partial) δ = 18.5 ($CHCH_3$), 44.1 (d, CHPh), 49.1 (d,

*C*HCH$_3$), 55.1 (CH$_2$N), 59.1 (OCH$_3$), 66.6 (NCH), 76.1 (*C*H$_2$OCH$_3$), 155.2 (C=N). - MS (70eV); *m/z* (%) = 536 (34) [M$^+$], 491 (100) [M$^+$–CH$_2$OCH$_3$], 422 (77), 295 (77), 182 (72), 127 (35) [C$_{10}$H$_7^+$]. - C$_{31}$H$_{41}$N$_2$O$_4$P (536.7): calcd. C 69.37, H 7.72, N 5.22; found C 69.07, H 7.89, N 5.00.

(2S,2'S,3'S/R)-(+)-1-[1'-Ethyl-4'-(diethoxyphosphoryl)-2'-methyl-3'-phenylbutylideneamino]-2-methoxymethylpyrrolidine [(*S,S,S*)-**4e**]: 1.98 g (10 mmol) 3-Pentanone SAMP hydrazone and 2.40 g (10 mmol) of diethyl [(*E*)-2-phenylethenyl]phosphonate were reacted according to general procedure 1, yielding 3.60 g of (*S,S,S/R*)-**4e** (82%) as a pale yellow oil after column chromatography. - *syn:anti* ratio was not determined. - $[\alpha]_D^{25}$ = +151.6 (neat). - IR (CHCl$_3$): $\tilde{\nu}$ = 3060 cm^{-1}, 3030, 2975, 2935, 2875, 1250 (P=O), 1100, 1035, 965. - ^{1}H NMR [(*S,S,S*)-**4e**]: δ = 0.70-1.16 (m, 9H, CCH$_2$C*H*$_3$, OCH$_2$C*H*$_3$), 1.18 (d, 3H, CHC*H*$_3$), 1.50-3.38 (m, 15H, CH$_2$CH$_2$, NCH$_2$, NC*H*C*H*$_2$OCH$_3$, C*H*C*H*C*H*$_2$P, CC*H*$_2$CH$_3$), 3.28 (s, 3H, OCH$_3$), 3.40-3.97 (m, 4H, OC*H*$_2$CH$_3$), 7.10-7.33 (m, 5H, arom.). - ^{13}C NMR: δ = 10.7 (H$_3$*C*CH$_2$C=N), 16.2 (2d, OCH$_2$*C*H$_3$), 16.9 (CH*C*H$_3$), 22.1, 26.7 (*C*H$_2$*C*H$_2$), 24.1 (H$_3$C*C*H$_2$C=N), 29.0 (d, CH$_2$P), 43.4 (d, *C*HCH$_2$P), 46.5 (d, *C*HCH$_3$), 54.6 (CH$_2$N), 59.0 (OCH$_3$), 61.1 (2d, O*C*H$_2$CH$_3$), 66.1 (NCH), 75.3 (*C*H$_2$OCH$_3$), 126.4, 127.9, 128.8 (CH arom.), 143.1 (C arom.), 172.8 (C=N); (*S,S,R*)-**4e** (partial) δ = 11.7 (H$_3$*C*CH$_2$C=N), 17.0 (CH*C*H$_3$), 22.2, 27.4 (*C*H$_2$*C*H$_2$), 24.2 (H$_3$C*C*H$_2$C=N), 31.5 (d, CH$_2$P), 40.5 (d, *C*HCH$_3$), 44.3 (d, *C*HCH$_2$P), 54.9 (CH$_2$N), 59.0 (OCH$_3$), 66.6 (NCH), 76.9 (*C*H$_2$OCH$_3$), 171.9 (C=N). - MS (70eV); *m/z* (%) = 438 (31) [M$^+$], 393 (100) [M$^+$–CH$_2$OCH$_3$], 324 (61), 197 (40). - C$_{23}$H$_{39}$N$_2$O$_4$P (438.6): calcd. C 62.98, H 8.98, N 6.39; found C 63.07, H 8.96, N 6.72.

(2S,3'S,4'R/S)-1-[4'-(Diethoxyphosphoryl)-1',3'-diisopropylpentylideneamino]-2-methoxymethylpyrrolidine [(*S,S,R/S*)-**7a**]: 0.99 g (5 mmol) 3-Methylbutanone SAMP hydrazone (*S*)-**2a** and 1.03 g (5 mmol) diethyl [(*E*)-3-methylbuten-1-yl]phosphonate were reacted according to general procedure 1. The *in situ* generated adduct anion was trapped with 0.52 ml (5.5 mmol) dimethyl sulfate at –78 °C, yielding 1.30 g of (*S,S,R/S*)-**7a** (62%) as a yellow oil after column chromatography. - *ds* = 85%. - ^{1}H NMR [(*E,S,S,R/S*)-**7a**]: δ = 0.89, 0.90 [2d, 6H, CHCH(C*H*$_3$)$_2$], 1.09, 1.12 [2d, 6H, CNCH(C*H*$_3$)$_2$], 1.16 (dd, 3H, CHC*H*$_3$), 1.33 (t, 6H, OCH$_2$C*H*$_3$), 1.45-3.44 (m, 15H, C*H*$_2$C*H*$_2$, NC*H*$_2$, NC*H*C*H*$_2$OCH$_3$, C*H*C*H*C*H*P, CNC*H*$_2$, CNC*H*), 3.30 (s, 3H, OCH$_3$), 4.00-4.22 (m, 4H, OC*H*$_2$CH$_3$); (*E,S,S,R/S*)-**7a** (partial)[17] δ = 3.32 (s, 3H, OCH$_3$). - ^{13}C NMR: δ = 10.2 (d, H$_3$*C*CHP), 16.6 (2d, OCH$_2$*C*H$_3$), 18.3, 20.7, 20.9, 21.2 [CH(*C*H$_3$)$_2$], 21.8, 26.7 (*C*H$_2$*C*H$_2$), 29.59 (d, N=C*C*H$_2$), 29.6 (d, *C*HP), 30.5 [d, *C*H(CH$_3$)$_2$], 33.8 [*C*H(CH$_3$)$_2$], 37.5 (d, *C*HCHP), 54.8 (CH$_2$N), 59.0 (OCH$_3$), 61.5 (2d, O*C*H$_2$CH$_3$), 65.7 (NCH), 75.3 (*C*H$_2$OCH$_3$), 176.3 (C=N). - MS (70eV); *m/z* (%) = 418 (26) [M$^+$], 373 (81) [M$^+$–CH$_2$OCH$_3$], 304 (65), 253 (100), 153 (47), 140 (62), 114 (65).

(2S,3'S,4'R/S)-(+)-1-[4'-(Diethoxyphosphoryl)-1',3'-diisopropyl-5'-phenylpentylideneamino]-2-methoxymethylpyrrolidine [(*S,S,R/S*)-**7b**]: 0.99 g (5 mmol) 3-Methylbutanone SAMP hydrazone (*S*)-**2a** and 1.03 g (5 mmol) diethyl [(*E*)-3-methylbuten-1-yl]phosphonate were reacted according to general procedure 1. The *in situ* generated adduct anion was trapped with 0.91 g (5.3 mmol) benzyl bromide at –78 °C, yielding 1.70 g of

(*S,S,R/S*)-**7b** (69%) as a pale yellow oil after column chromatography. - *ds* = 85%. - $[\alpha]_D^{25}$ = +25.2 (0.39, $CHCl_3$). - IR (film): $\tilde{\nu}$ = 3065 cm^{-1}, 3035, 2965, 2875, 1240 (P=O), 1100, 1035, 960, 700. - ^1H NMR [(*E,S,S,R/S*)-**7b**]: δ = 0.80-1.28 [m, 18H, OCH_2CH_3, $(H_3C)_2CHCN$, $(H_3C)_2CHCH$], 1.50-3.46 [m, 17H, CH_2CH_2, NCH_2, $NCHCH_2OCH_3$, CH_2CHCHP, $C_6H_5CH_2$, $(H_3C)_2CHCN$, $(H_3C)_2CH$], 3.32 (s, 3H, OCH_3), 3.63-4.13 (m, 4H, OCH_2CH_3), 7.12-7.33 (m, 5H, arom.); (*E,S,S,R/S*)-**7b** (partial)[17] δ = 3.23 (s, 3H, OCH_3). - ^{13}C NMR: δ = 16.3 (2d, OCH_2CH_3), 20.4, 20.8, 20.8, 21.0 ($CH(CH_3)_2$), 21.9, 26.9 (CH_2CH_2), 29.5 [d, $CH(CH_3)_2$], 29.9 (d, $N=CCH_2$), 32.4 (d, CH_2Ph), 33.3 [$(H_3C)_2CHC=N$], 38.7 (d, CHP), 39.5 (d, CHCHP), 54.8 (CH_2N), 59.0 (OCH_3), 61.0 (2d, OCH_2CH_3), 65.9 (NCH), 75.6 (CH_2OCH_3), 126.1, 128.2, 129.0 (CH arom.), 140.4 (C arom.), 174.9 (C=N). - MS (70eV); *m/z* (%) = 494 (14) [M^+], 449 (22) [$M^+-CH_2OCH_3$], 253 (100), 198 (50), 130 (63), 114 (51), 91 (77), 70 (56). - $C_{27}H_{47}N_2O_4P$ (494.7): calcd. C 65.54 H, 9.60, N 5.66; found C 65.34, H 9.66, N 5.94.

General procedure 2 for the ozonolysis of Michael adducts **4** *and Michael-Tandem adducts* **7**, *generating 4-oxophosphonates* **5** *and* **8**.

The hydrazones (10 mmol) were dissolved in CH_2Cl_2 (50 ml), and the solution was cooled to −78°C. A gentle stream of ozone was flushed through the solution until the latter turned blue, indicating the completion of the reaction. The excess ozone was removed from the solution by an argon stream and the mixture was allowed to warm to room temperature. The solvent was removed in vacuum and the nitrosamine (*S*)-**6** and the 4-oxophosphonates, respectively, were separated by column chromatography (silica gel; diethyl ether for nitrosamine isolation, acetonitrile/ethyl acetate 1:1 for phosphonate elution).

Diethyl (2R,3S)-(+)-(2-ethyl-3-methyl-4-oxo-4-phenylbutyl)phosphonate [(*R/S,S*)-**5a**]: 0.70 g (1.60 mmol) (*S,S,R/S*)-**4a** were reacted according to general procedure 2, yielding 0.47 g of (*R/S,S*)-**5a** (90%) as a yellow oil after column chromatography[18]. - *syn:anti* = 45:55. - IR (film): ν = 2980 cm^{-1}, 2940, 1680 (C=O), 1240 (P=O), 1030, 965, 700. - MS (70eV); *m/z* (%) = 326 (9) [M^+], 193 (47), 152 (64) [$H_3CPO(OC_2H_5)_2^+$], 125 (57), 105 (100) [$C_6H_5CO^+$], 77 (30) [$C_6H_5^+$]. - $C_{17}H_{27}O_4P$ (326.4): calcd. C 62.55, H 8.35; found C 62.26, H 8.45. - (*R,S*)-**5a** (*anti*): $[\alpha]_D^{25}$ = +36.8 (0.82, $CHCl_3$). - ^1H NMR: δ = 0.81 (t, 3H, $CHCH_2CH_3$), 1.14 (d, 3H, $CHCH_3$), 1.29, 1.34 (2t, 6H, OCH_2CH_3), 1.20-1.60 (m, 2H, $CHCH_2CH_3$), 1.72-1.99 (2m, 2H, CH_2P), 2.12-2.32 (m, 1H, $CHCH_2P$), 3.95 (m, 1H, $CHCH_3$), 4.03-4.22 (m, 4H, OCH_2CH_3), 7.42-7.59 (m, 3H, arom.), 8.04-8.12 (m, 2H, arom.). - ^{13}C NMR: δ = 11.2, 11.4 (CH_3), 16.4, 16.5 (2d, OCH_2CH_3), 23.1 (d, CH_2CH_3), 26.9 (d, CH_2P), 37.0 (d, $CHCH_2P$), 43.1 (d, $CHCH_3$), 61.5, 61.6 (2d, OCH_2CH_3), 128.6, 132.8 (CH arom.), 136.7 (C arom.), 203.8 (C=O). - (*S,S*)-**5a** (*syn*): $[\alpha]_D^{25}$ = +32.5 (1.10, $CHCl_3$). - ^1H NMR: δ = 1.04 (t, 3H, $CHCH_2CH_3$), 1.10 (d, 3H, $CHCH_3$), 1.12, 1.22 (2t, 6H, OCH_2CH_3), 1.39-1.95 (m, 4H, $CHCH_2CH_3$, CH_2P), 2.10-2.30 (m, 1H, $CHCH_2P$), 3.81 (ddq, $^4J_{P,H}$ = 1.7 Hz, 1H, $CHCH_3$), 3.84-4.05 (m, 4H, OCH_2CH_3), 7.42-7.59 (m, 3H, arom.), 7.90-8.00 (m, 2H, arom.). - ^{13}C NMR: δ = 10.9, 11.8 (CH_3), 16.2, 16.3 (2d, OCH_2CH_3), 25.5 (d, CH_2CH_3), 25.7 (d, CH_2P), 36.9 (d, $CHCH_2P$), 41.4 (d, $CHCH_3$), 61.3, 61.4 (2d, OCH_2CH_3), 128.3, 128.7, 132.9 (CH arom.), 136.6 (C arom.), 203.6 (C=O).

Diethyl (2R/S,3S)-(+)-(2-isopropyl-3-methyl-4-oxo-4-phenylbutyl)phosphonate [(*R/S,S*)-**5b**]: 2.46 g (10 mmol) Propiophenone SAMP hydrazone and 2.06 g (10 mmol) diethyl [(*E*)-3-methylbuten-1-yl]phosphonate were combined according to general procedure 1. The crude Michael adduct was further reacted according to general procedure 2, yielding 2.80 g of (*R/S,S*)-**5b** (82%) as a yellow oil after column chromatography[18]. - *syn*:*anti* = 33:67. - IR (film): ν = 3060 cm^{-1}, 2980, 2905, 1680 (C=O), 1245 (P=O), 1030, 965. - MS (70eV); *m/z* (%) = 340 (7) [M^+], 297 (37) [M^+–$CH(CH_3)_2$], 207 (85), 152 (25) [$H_3CPO(OC_2H_5)_2^+$], 105 (100) [$C_6H_5CO^+$], 77 (25) [$C_6H_5^+$]. - $C_{18}H_{29}O_4P$ (340.4): calcd. C 63.50, H 8.60; found C 63.12, H 8.66. - (*R,S*)-**5b** (*anti*): $[\alpha]_D^{25}$ = +33.7 (1.01, $CHCl_3$). - ^1H NMR: δ = 0.74, 0.87 [2d, 6H, $CH(CH_3)_2$], 1.22 (d, 3H, $CHCH_3$), 1.30, 1.34 (2t, 6H, OCH_2CH_3), 1.77-2.02 [m, 3H, CH_2P, $CH(CH_3)_2$], 2.20-2.35 (m, 1H, $CHCH_2P$), 3.96 (dq, 1H, $COCHCH_3$), 4.02-4.24 (m, 4H, OCH_2CH_3), 7.42-7.58 (m, 3H, arom.), 8.00-8.10 (m, 2H, arom.). - ^{13}C NMR: δ = 12.5 ($CHCH_3$), 16.5, 16.5 (2d, OCH_2CH_3), 19.5, 22.0 [$CH(CH_3)_2$], 24.3 (d, CH_2P), 28.8 [d, $CH(CH_3)_2$], 40.8, 43.2 (d, $CHCH_2P$, $CHCH_3$), 61.5 (d, OCH_2CH_3), 128.5, 128.6, 132.7 (CH arom.), 137.0 (C arom.), 204.4 (C=O). - ^{31}P NMR: δ = 32.2. - (*S,S*)-**5b** (*syn*): $[\alpha]_D^{25}$ = +30.9 (1.00, $CHCl_3$). - ^1H NMR: δ = 0.94, 1.00 [2d, 6H, $CH(CH_3)_2$], 1.17, 1.26 (2t, 6H, OCH_2CH_3), 1.61-2.02 [m, 3H, $CH(CH_3)_2$, CH_2P], 2.16-2.34 (m, 1H, $CHCH_2P$), 3.74 (m, 1H, $COCHCH_3$), 3.85-4.13 (m, 4H, OCH_2CH_3), 7.42-7.60 (m, 3H, arom.), 7.93-8.00 (m, 2H, arom.). - ^{13}C NMR: δ = 13.6 ($CHCH_3$), 16.3 (2d, OCH_2CH_3), 19.9, 20.2 [$CH(CH_3)_2$], 23.7 (d, CH_2P), 30.9 [d, $CH(CH_3)_2$], 40.2, 41.4 (d, $CHCH_2P$, $CHCH_3$), 61.40, 61.43 (d, OCH_2CH_3), 128.3, 128.7, 132.9 (CH arom.), 136.6 (C arom.), 203.6 (C=O). - ^{31}P NMR: δ = 31.9.

Diethyl (2S,3S)-(+)-(3-methyl-4-oxo-2,4-diphenylbutyl)phosphonate [(*R/S,S*)-**5c**]: 1.50 g (3.09 mmol) Hydrazone **4c** were reacted according to general procedure 2, yielding. 1.10 g of (*R/S,S*)-**5c** (95%) as a yellow oil after column chromatography. - *syn*:*anti* = 21:79. - α_D^{25} = +29.0 (neat) [(*S,S*)-**5c** (*anti*): $[\alpha]_D^{25}$ = +20.4 (0.97, $CHCl_3$); (*R,S*)-**5c** (*syn*): $[\alpha]_D^{25}$ = +35.0 (0.66, $CHCl_3$)][18]. - IR (film): ν = 3060 cm^{-1}, 3030, 2980, 1680 (C=O), 1250 (P=O), 1035, 965, 700. - ^1H NMR [(*S,S*)-**5c** (*anti*)]: δ = 1.03, 1.05 (2t, 6H, OCH_2CH_3), 1.24 (d, 3H, $CHCH_3$), 2.10-2.42 (m, 2H, CH_2P), 3.47-3.95 (m, 6H, OCH_2CH_3, $CHCHCH_2P$), 7.04-8.06 (m, 10H, arom.); (*R,S*)-**5c** (partial) δ = 0.94 (d, 3H, $CHCH_3$), 1.13 (t, 6H, OCH_2CH_3). - ^{13}C NMR: δ = 14.6 ($CHCH_3$), 16.1 (2d, OCH_2CH_3), 27.8 (d, CH_2P), 42.5 (d, $CHCH_2P$), 46.8 (d, $CHCH_3$), 61.1, 61.3 (2d, OCH_2CH_3), 126.7, 128.1, 128.2, 128.4, 128.5, 132.8 (CH arom.), 136.8, 142.3 (C arom.), 202.8 (C=O). - MS (70eV); *m/z* (%) = 374 (29) [M^+], 269 (88) [M^+– C_6H_5CO], 152 (30) [$H_3CPO(OC_2H_5)_2^+$], 105 (100) [$C_6H_5CO^+$], 77 (57) [$C_6H_5^+$]. - $C_{21}H_{27}O_4P$ (374.5): calcd. C 67.35, H 7.28; found C 67.48, H 7.24.

Diethyl (2S,3S)-(–)-[3-methyl-4-(2'-naphthyl)-4-oxo-2-phenylbutyl]phosphonate [(*R/S,S*)-**5d**]: 0.154 g (0.287 mmol) Hydrazone **4d** were reacted according to general procedure 2, yielding 0.093 g of (*R/S,S*)-**5d** (76%) as a yellow oil after column chromatography. - *syn*:*anti* = 13:87. - $[\alpha]_D^{25}$ = –28.2 (0.72, $CHCl_3$) [(*S,S*)-**5d** (*anti*): $[\alpha]_D^{25}$ = –42.0 (0.91, $CHCl_3$); (*R,S*)-**5d** (*syn*): $[\alpha]_D^{25}$ = +39.0 (0.30, $CHCl_3$)][18]. - IR ($CHCl_3$): ν = 3060 cm^{-1}, 2985, 1675 (C=O), 1240 (P=O), 1035, 965. - ^1H NMR [(*S,S*)-**5d** (*anti*)]: δ = 1.02,1.06 (2t, 6H, OCH_2CH_3),

1.32 (d, 3H, CHC$\boldsymbol{H}_3$), 2.10-2.50 (m, 2H, C$\boldsymbol{H}_2$P), 3.50-3.94 (m, 5H, OC$\boldsymbol{H}_2$CH$_3$, C$\boldsymbol{H}$C$_6$H$_5$), 4.00 (ddq, 1H, C$\boldsymbol{H}$CH$_3$), 7.00-8.60 (m, 12H, arom.); (*R,S*)-**5d** (partial) δ = 1.02 (d, 3H, CHC$\boldsymbol{H}_3$), 1.14 (t, 6H, OCH$_2$C$\boldsymbol{H}_3$). - ^{13}C NMR: δ = 14.9 (CH$\boldsymbol{C}$H$_3$), 16.0, 16.2 (2d, OCH$_2$$\boldsymbol{C}H_3$), 27.9 (d, CH$_2$P), 42.64 (d, CHPh), 46.8 (d, $\boldsymbol{C}$HCH$_3$), 61.2, 61.3 (2d, O$\boldsymbol{C}$H$_2$CH$_3$), 123.6-131.0 (CH arom.), 132.4, 134.0, 135.4, 142.3 (C arom.), 202.8 (C=O). - MS (70eV); *m/z* (%) = 424 (20) [M$^+$], 269 (63) [M$^+$–C$_{10}$H$_7$CO], 155 (100) [C$_{10}$H$_7$CO$^+$], 152 (21) [H$_3$CPO(OC$_2$H$_5$)$_2^+$], 127 (42) [C$_{10}$H$_7^+$]. - C$_{25}$H$_{29}$O$_4$P (424.5): calcd. C 70.73, H 6.90; found C 70.57, H 6.92.

Diethyl (2S,3S)-(+)-(3-methyl-4-oxo-2-phenylhexyl)phosphonate [(*S,S*)-**5e**]: 1.34 g (3.06 mmol) Hydrazone **4e** were reacted according to general procedure 2, yielding 0.95 g of (*S,S*)-**5e** (95%) as a yellow oil after column chromatography. - *syn*:*anti* = 21:79. - α_D^{25} = +32.6 (neat). - IR (film): ν = 3060 cm^{-1}, 3030, 2980, 1710 (C=O), 1245 (P=O), 1030, 965. - ^{1}H NMR [(*S,S*)-**5e** (*anti*)]: δ = 0.78 (t, 3H, CCH$_2$C$\boldsymbol{H}_3$), 1.08, 1.09 (2t. 6H, OCH$_2$C$\boldsymbol{H}_3$), 1.14 (d, 3H, CHC$\boldsymbol{H}_3$), 1.90-2.64 (m, 4H, CC$\boldsymbol{H}_2$CH$_3$, C$\boldsymbol{H}_2$P), 2.84 (dq, *J* = 8.6 Hz, *J* = 6.9 Hz, 1H, C$\boldsymbol{H}$CH$_3$), 3.30 (m, 1H, C$\boldsymbol{H}$CH$_2$P), 3.57-3.94 (m, 4H, OC$\boldsymbol{H}_2$CH$_3$,), 7.14-7.34 (m, 5H, arom.); (*R,S*)-**5e** (partial) δ = 0.84 (d, 3H, CHC$\boldsymbol{H}_3$). - ^{13}C NMR: δ = 7.4 (H$_3$$\boldsymbol{C}CH_2$C=O), 14.4 (CH$\boldsymbol{C}H_3$), 16.1 (2d, OCH$_2$$\boldsymbol{C}H_3$), 28.4 (d, CH$_2$P), 35.8 (H$_3C\boldsymbol{C}H_2$C=O), 42.8 (d, $\boldsymbol{C}$HCH$_2$P), 52.6 (d, $\boldsymbol{C}$HCH$_3$), 61.3 (2d, O$\boldsymbol{C}$H$_2$CH$_3$), 126.9, 128.3, 128.3 (CH arom.), 142.0 (C arom.), 213.7 (C=O). - MS (70eV); *m/z* (%) = 326 (33) [M$^+$], 269 (79) [M$^+$–H$_3$CCH$_2$CO], 152 (100) [H$_3$CPO(OC$_2$H$_5$)$_2^+$], 57 (21) [H$_3$CCH$_2$CO$^+$]. - C$_{17}$H$_{27}$O$_4$P (326.4): calcd. C 62.55, H 8.35; found C 62.33, H 8.42.

Diethyl (1R/S,2S)-(+)-(2-isopropyl-1,5-dimethyl-4-oxohexyl)phosphonate [(*R/S,S*)-**8a**]: 0.99 g (5 mmol) 3-Methylbutanone SAMP hydrazone (*S*)-**2a** and 1.03 g (5 mmol) of diethyl [(*E*)-3-methylbuten-1-yl]phosphonate were combined according to general procedure 1. The *in situ* generated adduct anion was trapped with 0.34 ml (5.5 mmol) CH$_3$I at –78°C. The crude tandem product was cleaved according to general procedure 2, yielding 0.95 g of (*R/S,S*)-**8a** (62%) as a yellow oil after column chromatography. - *de* = 53%. - α_D^{25} = +4.9 (neat). - When dimethyl sulfate (0.52 ml, 5.5 mmol) was used as trapping reagent, 1.00 g of (*R/S,S*)-**8a** (65%) was isolated as a yellow oil after column chromatography. - *de* = 66%. - IR (film): ν = 2970 cm^{-1}, 1715 (C=O), 1240 (P=O), 1030, 960. - ^{1}H NMR[19]: δ = 0.82, 0.89 {0.77, 0.91} [2d, 6H, ($\boldsymbol{H}_3$C)$_2$CHCH], 1.10 [d, 6H, ($\boldsymbol{H}_3$C)$_2$CHCO], 1.12 (dd, $^3J_{P,H}$ = 19.1 Hz, 3H, $\boldsymbol{H}_3$CCHP), 1.31 {1.32} (t, 6H, OCH$_2$C$\boldsymbol{H}_3$), 1.61 [dsept. 1H, CHC$\boldsymbol{H}$(CH$_3$)$_2$], 1.96-2.20 (ddq, $^2J_{P,H}$ = 24.0 Hz, $^3J_{H,H}$ = 2.2 Hz, $^3J_{H,H}$ = 7.2 Hz, 1H, C$\boldsymbol{H}$P), 2.34-3.02 (m, 3H, C$\boldsymbol{H}$C$\boldsymbol{H}_2$CO), 2.65 [sept, 1H, (H$_3$C)$_2$C$\boldsymbol{H}$CO], 3.98-4.18 (m, 4H, OC$\boldsymbol{H}_2$CH$_3$). - ^{13}C NMR: δ = 9.1 (d, H$_3$$\boldsymbol{C}$CHP), 16.5 (2d, OCH$_2$$\boldsymbol{C}H_3$), 18.5, 18.7, 20.2, 20.7 [CH($\boldsymbol{C}$H$_3$)$_2$], 30.90 (d, H$_3$C$\boldsymbol{C}$HP), 30.92 y(d, $\boldsymbol{C}$H(CH$_3$)$_2$], 36.7 (d, $\boldsymbol{C}$HCHP), 40.6 (d, O=C$\boldsymbol{C}$H$_2$), 40.8 [d, (H$_3$C)$_2$$\boldsymbol{C}$HC=O], 61.3, 61.9 (2d, O$\boldsymbol{C}H_2CH_3$), 213.3 (C=O). - MS (70eV); *m/z* (%) = 306 (3) [M$^+$], 263 (100) [M$^+$–(H$_3$C)$_2$CH], 166 (64) [H$_3$CCH$_2$PO(OC$_2$H$_5$)$_2^+$]. - C$_{15}$H$_{31}$O$_4$P (306.4): calcd. C 58.79, H 10.22; found C 58.78, H 10.14.

Diethyl (1R/S,2S)-(+)-(2-tert-butyl-1,5-dimethyl-4-oxohexyl)phosphonate [(*R/S,S*)-**8b**]: 0.99 g (5 mmol) 3-Methylbutanone SAMP hydrazone (*S*)-**2a** and 1.03 g (5 mmol) of diethyl [(*E*)-3,3-dimethylbuten-1-yl]phos-

phonate were combined according to general procedure 1. The *in situ* generated adduct anion was trapped with 0.34 ml (5.5 mmol) CH_3I at -100°C. The crude tandem product was cleaved according to general procedure 2, yielding 1.10 g of (*R/S,S*)-**8b** (69%) as a yellow oil after column chromatography. - *de* = 77%. - α_D^{25} = +3.9 (neat). - IR (film): ν = 2970 cm^{-1}, 2910, 1715 (C=O), 1240 (P=O), 1030, 960. - ^1H NMR[19]: δ = 0.85 {0.91} [s, 9H, $(\boldsymbol{H}_3C)_3C$], 1.11, 1.12 [2d, 6H, $(\boldsymbol{H}_3C)_2CH$], 1.18 (dd, $^3J_{P,H}$ = 19.8 Hz, 3H, $\boldsymbol{H}_3CCHP$), 1.31 (t, 6H, $OCH_2C\boldsymbol{H}_3$), 2.06-2.26 (ddq, $^2J_{P,H}$ = 24.8 Hz, $^3J_{H,H}$ = 1.0 Hz, $^3J_{H,H}$ = 7.4 Hz, 1H, C*H*P), 2.45-2.57 (dd, 1H, C*H*HCO), 2.57-2.76 [m, 3H, $(H_3C)_2C\boldsymbol{H}$, $CH\boldsymbol{H}CO$, $C\boldsymbol{H}C(CH_3)_3$], 4.00-4.22 (m, 4H, $OC\boldsymbol{H}_2CH_3$). - ^{13}C NMR: δ = 10.6 (d, $H_3\boldsymbol{C}CHP$), 16.5 (2d, $OCH_2\boldsymbol{C}H_3$), 18.7, 18.8 [$CH(\boldsymbol{C}H_3)_2$], 28.1 [$C(\boldsymbol{C}H_3)_3$], 29.9 (d, $H_3C\boldsymbol{C}HP$), 35.2 [d, $\boldsymbol{C}(CH_3)_3$], 38.0 [d, s, $\boldsymbol{C}HCHP$, $(H_3C)_2\boldsymbol{C}HC{=}O$], 38.1 (d, $O{=}C\boldsymbol{C}H_2$), 61.4, 62.1 (2d, $O\boldsymbol{C}H_2CH_3$), 212.7 (C=O). - ^{31}P NMR: 34.7 {34.0}. - MS (70eV); *m/z* (%) = 320 (4) [M^+], 277 (100) [M^+–$(H_3C)_2CH$], 221 (31), 193 (30), 166 (29) [$H_3CCH_2PO(OC_2H_5)_2^+$]. - $C_{16}H_{33}O_4P$ (320.5): calcd. C 59.96, H 10.40; found C 59.62, H 10.29.

Diethyl (1R/S,2S)-(+)-(1,5-dimethyl-4-oxo-2-phenylhexyl)phosphonate [(*R/S,S*)-**8c**]: 1.98 g (10 mmol) 3-Methylbutanone SAMP hydrazone (*S*)-**2a** and 2.40 g (10 mmol) diethyl [(*E*)-2-phenylethenyl]phosphonate were combined according to general procedure 1. The *in situ* generated adduct anion was trapped with 0.65 ml (10.5 mmol) CH_3I at -100°C. The crude tandem product was cleaved according to general procedure 2, yielding 1.30 g of (*R/S,S*)-**8c** (38%) as a yellow oil after column chromatography. - *de* = 50%. - α_D^{25} = +0.02 (neat). - IR (film): ν = 3060 cm^{-1}, 3030, 2980, 1715 (C=O), 1235 (P=O), 1030, 960. - ^1H NMR[19]: δ = 0.98, 1.03 {0.83, 0.95} [2d, 6H, $(\boldsymbol{H}_3C)_2CH$], 1.15 {0.96} (dd, $^3J_{P,H}$ = 18.1 Hz, 3H, $\boldsymbol{H}_3CCHP$), 1.21, 1.30 (2t, 6H, $OCH_2C\boldsymbol{H}_3$), 2.14 (ddq, $^2J_{P,H}$ = 21.5 Hz, $^3J_{H,H}$ = 3.7 Hz, $^3J_{H,H}$ = 7.4 Hz, 1H, C*H*P), 2.56 {2.42} [sept, 1H, $C\boldsymbol{H}(CH_3)_2$], 3.02-3.15 (dd, 1H, C*H*HCO), 3.20-3.32 (dd, 1H, $CH\boldsymbol{H}CO$), 3.68-3.84 (m, 1H,$C\boldsymbol{H}CHP$), 3.92-4.17 (m, 4H, $OC\boldsymbol{H}_2CH_3$), 7.10-7.32 (m, 5H, arom.). - ^{13}C NMR: δ = 10.2 (d, $H_3\boldsymbol{C}CHP$), 16.9 (2d, $OCH_2\boldsymbol{C}H_3$), 18.0, 18.1 [$CH(\boldsymbol{C}H_3)_2$], 36.6 (d, $H_3C\boldsymbol{C}HP$), 39.6 (d, $\boldsymbol{C}HCHP$), 40.9 [$(H_3C)_2\boldsymbol{C}HC{=}O$], 41.0 (d, $O{=}C\boldsymbol{C}H_2$), 61.4, 61.7 (2d, $O\boldsymbol{C}H_2CH_3$), 126.6, 128.0, 128.2 (CH arom.), 142.5 (d, C arom.), 212.6 (C=O). - MS (70eV); *m/z* (%) = 340 (30) [M^+], 269 (100) [M^+–$(H_3C)_2CHCO$], 241 (46), 166 (47) [$H_3CCH_2PO(OC_2H_5)_2^+$]. - $C_{18}H_{29}O_4P$ (340.4): calcd. C 63.50, H 8.60; found C 62.39, H 8.83.

Diethyl (1R/S,2S)-(1-ethyl-2-isopropyl-5-methyl-4-oxohexyl)phosphonate [(*R/S,S*)-**8d**]: 0.99 g (5 mmol) 3-Methylbutanone SAMP hydrazone (*S*)-**2a** and 1.03 g (5 mmol) diethyl [(*E*)-3-methylbuten-1-yl]phosphonate were combined according to general procedure 1. The *in situ* generated adduct anion was trapped with 0.41 ml (5.05 mmol) C_2H_5I at –78°C. The crude tandem product was cleaved according to general procedure 2, yielding 0.90 g of (*R/S,S*)-**8d** (56%) as a yellow oil after column chromatography. - *de* = 10%. - IR (film): $\tilde{\nu}$ = 2970 cm^{-1}, 2940, 1715 (C=O), 1240 (P=O), 1030, 960. - ^1H NMR[20]: δ = 0.76, 0.83, 0.91, 0.94 [4d, 12H, $(\boldsymbol{H}_3C)_2CHCH$], 1.02, 1.08 (2t, 6H, $OCH_2C\boldsymbol{H}_3$), 1.07-1.14 [m, 12H, $(\boldsymbol{H}_3C)_2CHCO$], 1.31, 1.32, 1.33 (3t, 12H, $OCH_2C\boldsymbol{H}_3$), 1.40-2.00 [m, 6H, $(H_3C)_2C\boldsymbol{H}CH$, $CC\boldsymbol{H}_2CH_3$], 2.10-3.05 [m, 10H, $C\boldsymbol{H}C\boldsymbol{H}C\boldsymbol{H}_2CO$, $(H_3C)_2C\boldsymbol{H}CO$], 3.98-4.20 (m, 8H, $OC\boldsymbol{H}_2CH_3$). - ^{13}C NMR: δ = 13.0, 14.1 (2d, $H_3\boldsymbol{C}CH_2$), 16.5 (m,

$OCH_2\boldsymbol{C}H_3$), 18.5, 18.5, 18.6, 18.7, 20.6, 20.6, 20.7, 21.8 [$CH(\boldsymbol{C}H_3)_2$], 21.1 (d, $H_3C\boldsymbol{C}H_2$), 30.7, 30.9 [2d, $\boldsymbol{C}H(CH_3)_2$], 37.4, 38.2 (2d, $\boldsymbol{C}$HCHP), 38.3, 38.7 (2d, $\boldsymbol{C}$HP), 40.8, 40.9 [$(H_3C)_2\boldsymbol{C}HC{=}O$], 41.0, 41.1 (2d, $O{=}C\boldsymbol{C}H_2$), 61.2 (m, $O\boldsymbol{C}H_2CH_3$), 213.4, 213.9 (C=O). - MS (70eV); *m/z* (%) = 320 (2) [M^+], 277 (100) [M^+–$(H_3C)_2CH$], 221 (35), 180 (54) [$H_3CCH_2CH_2PO(OC_2H_5)_2^+$]. - $C_{16}H_{33}O_4P$ (320.5): calcd. C 59.96, H 10.40; found C 59.19, H 10.42.

Diethyl (1R/S,2S)-(–)-(1-benzyl-2-isopropyl-5-methyl-4-oxohexyl)phosphonate [(*R/S,S*)-**8e**]: 0.98 g (1.98 mmol) Hydrazone **7b** were reacted according to general procedure 2, yielding 0.63 g of (*R/S,S*)-**8e** (83%) as a yellow oil after column chromatography. - *de* = 30%. - α_D^{25} = –10.2 (neat). - $[\alpha]_D^{25}$ = –8.1 (1.53, $CHCl_3$). - IR (film): $\tilde{\nu}$ = 3065 cm^{-1}, 3015, 2970, 2940, 2910, 1715 (C=O), 1240 (P=O), 1030, 960. - ^{1}H NMR[19]: δ = 0.83, 0.91 {0.65, 0.74} [2d, 6H, $(\boldsymbol{H}_3C)_2$CHCH], 1.10, 1.12 {1.11, 1.14} [2d, 6H, $(\boldsymbol{H}_3C)_2$CHCO], 1.07, 1.25 {1.30, 1.31} (2t, 6H, $OCH_2C\boldsymbol{H}_3$), 1.68 {1.90} [dsept, 1H, $(H_3C)_2C\boldsymbol{H}$CH], 2.05-3.20 [m, 7H, $(H_3C)_2C\boldsymbol{H}$CO, $C\boldsymbol{H}_2C\boldsymbol{H}C\boldsymbol{H}$P, $C\boldsymbol{H}_2C_6H_5$], 3.69-4.15 (m, 4H, $OC\boldsymbol{H}_2CH_3$), 7.14-7.34 (m, 5H, arom.). - ^{13}C NMR: δ = 16.4 (2d, $OCH_2\boldsymbol{C}H_3$), 18.6, 18.6, 20.5, 21.3 [$CH(\boldsymbol{C}H_3)_2$], 30.3 [d, $\boldsymbol{C}H(CH_3)_2$], 31.4 (d, $\boldsymbol{C}H_2$Ph), 37.7 (d, $\boldsymbol{C}$HCHP), 39.1 (d, $\boldsymbol{C}$HP), 40.8 [$(H_3C)_2\boldsymbol{C}HC{=}O$], 41.0 (d, $O{=}C\boldsymbol{C}H_2$), 61.2 (2d, $O\boldsymbol{C}H_2CH_3$), 126.2, 128.2, 129.0 (CH arom.), 140.3 (d, C arom.), 213.3 (C=O). - MS (70eV); *m/z* (%) = 382 (10) [M^+], 339 (56) [M^+–$(H_3C)_2CH$], 297 (49), 242 (44), 241 (100) [$C_6H_5CH_2CHPO(OC_2H_5)_2^+$], 91 (48) [$C_6H_5CH_2^+$]. - $C_{21}H_{35}O_4P$ (382.5): calcd. C 65.93, H 9.24; found C 65.89, H 9.62.

2-Ethoxy-4-isopropyl-1-[(2S)-2-(methoxymethyl)pyrrolidinyl]-1,2,3,4,4a,5,6,7-octahydro-1,2λ⁵-benzazaphosphinin-2-one (**11**): 1.05 g (5 mmol) Cyclohexanone SAMP hydrazone (*S*)-**2b** and 1.03 g (5 mmol) [(*E*)-3-methylbuten-1-yl]phosphonate were reacted according to general procedure 1, the mixture was allowed to warm to room temperature before hydrolysis, yielding 0.90 g of **11** (49%) as yellow oil after column chromatography. - *ds* = >90%. - $[\alpha]_D^{25}$ = +32.4 (0.91, $CHCl_3$). - IR (film): ν = 2955 cm^{-1}, 2930, 2875, 1655 (C=C), 1040, 950. - ^{1}H NMR: δ = 0.92, 0.96 [2d, 6H, $(\boldsymbol{H}_3C)_2$CH], 1.31 (t, 3H, $OCH_2C\boldsymbol{H}_3$), 1.38-2.15 [m, 14H, $NCH_2C\boldsymbol{H}_2C\boldsymbol{H}_2$, $C\boldsymbol{H}_2C\boldsymbol{H}_2C\boldsymbol{H}_2$, $(H_3C)_2C\boldsymbol{H}C\boldsymbol{H}C\boldsymbol{H}_2$P], 2.55-3.70 (m, 6H, $NC\boldsymbol{H}_2$, $NC\boldsymbol{H}C\boldsymbol{H}_2OCH_3$, $NCC\boldsymbol{H}$CH), 3.33 (s. 3H, $OC\boldsymbol{H}_3$), 3.98-4.17 (m, 2H, $OC\boldsymbol{H}_2CH_3$), 5.30-5.45 (s, 1H, NC=C***H***). - ^{13}C NMR: δ = 16.6 (d, $OCH_2\boldsymbol{C}H_3$), 18.6, 22.8 [$C(\boldsymbol{C}H_3)_2$)] 22.0, 22.4, 24.3, 27.2, 27.6 ($CH_2CH_2CH_2$, CH_2CH_2), 26.5 (d, CH_2P), 27.7 (d, $\boldsymbol{C}HCH_2$P), 38.2 (=CCH), 41.0 (d, $\boldsymbol{C}HCH_2$P), 50.5 (CH_2N), 59.0 (OCH_3), 60.9 ($O\boldsymbol{C}H_2CH_3$, NCH), 75.3 ($\boldsymbol{C}H_2OCH_3$), 106.0 (***C***H=C), 139.0 (CH=***C***). - MS (70eV); *m/z* (%) = 370 (17) [M^+], 325 (100) [M^+–CH_2OCH_3]. - $C_{19}H_{35}N_2O_3P$ (370.5): calcd. C 61.58, H 9.54, N 7.56; found C 61.33, H 9.65, N 7.77.

2-Ethoxy-4-isopropyl-1-[(2S)-2-(methoxymethyl)pyrrolidinyl]-1,2,3,4,5,6,7,8-octahydro-1,2λ⁵-benzazaphosphinin-2-one (**12**): Upon heating or storing **11** for a longer period of time at room temperature, **7** was isomerised to the enhydrazine **12**, which was separated as an oil by column chromatography (silica gel; acetonitrile/ethyl acetate 1:1). - $[\alpha]_D^{25}$ = +100.6 (1.16, $CHCl_3$). - IR (film): ν = 2955 cm^{-1}, 2925, 2875, 1645 (C=C), 1255, 1045. - ^{1}H NMR: δ = 0.75, 0.90 [2d, 6H, $(\boldsymbol{H}_3C)_2$CH], 1.26 (t, 3H, $OCH_2C\boldsymbol{H}_3$), 1.25-3.93 [m, 21H,

NC***H***$_2$C***H***$_2$C***H***$_2$, C***H***$_2$C***H***$_2$C***H***$_2$C***H***$_2$, NC***H***C***H***$_2$OCH$_3$, (H$_3$C)$_2$C***H***C***H***C***H***$_2$P], 3.33 (s, 3H, OC***H***$_3$), 3.93-4.15 (m, 2H, OC***H***$_2$CH$_3$). - ^{13}C NMR: δ = 15.4, 20.7 [C(***C***H$_3$)$_2$], 16.4 (d, OCH$_2$***C***H$_3$), 22.1, 23.2, 23.4, 26.8, 27.2, 29.5 (CH$_2$CH$_2$CH$_2$CH$_2$, CH$_2$CH$_2$), 24.6 (d, CH$_2$P), 27.4 (d, ***C***HCH$_2$P), 45.5 (=CCH), 51.6 (CH$_2$N), 59.0 (OCH$_3$), 59.8 (d, O***C***H$_2$CH$_3$), 62.5 (NCH), 75.4 (***C***H$_2$OCH$_3$), 117.9 (NC≡***C***), 136.4 (d, N***C***=C). - MS (70eV); *m/z* (%) = 370 (24) [M$^+$], 325 (72) [M$^+$ - CH$_2$OCH$_3$], 256 (100), 228 (41), 214 (94). - C$_{19}$H$_{35}$N$_2$O$_3$P (370.5): calcd. C 61.58, H 9.54, N 7.56; found C 61.91, H 9.36, N 7.71.

REFERENCES AND NOTES

1. For some examples see: Enders, D.; Wahl, H.; Papadopoulos, K. *Liebigs Ann.* **1995**, 1177-1184.
2. Minowa, N.; Hirayama, M.; Fukatsu, S. *Tetrahedron Lett.* **1984**, *25*, 1147-1150.
3. Ruiz, M.; Ojea, V.; Shapiro, G.; Weber, H.-P. *Tetrahedron Lett.* **1994**, *35*, 4551-4554.
4. For asymmetric cis dihydroxylation of phosphonates see for example: Lohray, B. B.; Maji, D. K.; Nandanan, E. *Ind. J. Chem. Sect. B* **1995**, *34*, 1023-1025.
5. For the asymmetric synthesis of aminophosphonates see for example: Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J.; Wieczorek, M. W.; Blaszczyk, J. *Chem. Comm.* **1996**, 1503-1504.
6. Enders, D.; Eichenauer, H. *Angew. Chem.* **1976**, *88*, 579-581. - Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933-2960.
7. Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967-4970. - Enders, D.; Rendenbach, B. E. M. Tetrahedron **1986**, 42, 2235-2242. - Enders, D.; Papadopoulos, K.; Rendenbach, B. E. M.; Appel, R.; Knoch, F. *Tetrahedron Lett.* **1986**, *72*, 3491-3494. - Enders, D.; Rendenbach, B. E. M. *Chem. Ber.* **1987**, *120*, 1223-1227. - Enders, D.; Rendenbach, B. E. M. In *Enantioselective Synthesis of Bioregulators in Pesticide Science and Biotechnology*; Greengalph, R.; Roberts, T. R. Eds.; Blackwell Scientific Publishers, Oxford, **1987**, p. 17. - Enders, D.; Demir, A. S.; Rendenbach, B. E. M. *Chem. Ber.* **1987**, *120*, 1731-1735. - Enders, D.; Demir, A. S.; Puff, H.; Franken, S. *Tetrahedron Lett.* **1987**, *28*, 3795-3798. - Enders, D.; Müller, S.; Demir, A. S. Tetrahedron Lett. **1988**, *29*, 6437-6440. - Enders, D.; Scherer, H. J.; Raabe, G. *Angew. Chem.* **1991**, *103*, 1676-1678; *Angew. Chem Int. Ed. Engl.* **1991**, *30*, 1664-1666. - Enders, D.; Scherer, H. J.; Runsink, J. *Chem. Ber.* **1993**, *126*, 1929-1944. - Enders, D.; Papadopoulos, K.; Herdtweck, E. *Tetrahedron* **1993**, *49*, 1821-1830. Enders, D.; Bartzen, D. *Liebigs Ann. Recueil* **1997**, 1089-1100.
8. For reviews on the SAMP/RAMP hydrazone method see: Enders, D. In *Asymmetric Synthesis*; Morrison, J. D. Ed.; Academic Press, Orlando, **1984**, Vol. 3B, p. 275. - Enders, D.; Klatt, M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A. Ed.; Wiley, New York, **1995**, p. 3368.
9. *ee* Values were deduced from the *ds* values of hydrazones **4**.
10. Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337-1361. - Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1362-1383.
11. For a short review see: Teulade, M.-P.; Savignac, P. *Janssen Chimica Acta* **1988**, *6*, 3 and references cited therein.

12. Mikolajczyk, M.; Grzejszczak, S.; Midura, W.; Zatorski, A. *Synthesis* **1976**, 396-398. - Gloyna, D.; Köppel, H.; Henning, H.-G. *J. Prakt. Chem.* **1974**, *316*, 832-838.
13. Czekanski, T.; Gross, H.; Costisella, B. *J. Prakt. Chem.* **1982**, *324*, 537-544.
14. Papadopoulos, K. Ph. D. Thesis, University of Bonn, **1985**.
15. Rotations were measured on the (*E*)/(*Z*) isomers. The isomers along the C-N double bond were equilibrated upon heating the hydrazones to 90 to 110°C for 4 h.
16. No diastereomers with (*R*) configuration at stereocenter C-2' were detected by ^{13}C NMR spectroscopy or analytical HPLC.
17. Resonance of the minor isomers are given. Configurations were not determined.
18. The *anti* and *syn* isomers were separated by preparative HPLC.
19. NMR data of the major diastereomer are given and significant chemical shifts of the minor are added in brackets {}.
20. NMR data of both diastereomers are given.

(*Received in Germany* 19 *June* 1997; *accepted* 11 *July* 1997)