ISSN 0018-019X

Erscheint 9mal jährlich - Paraît 9 fois par an

192. Asymmetric Synthesis of α-Aminophosphonic Acids by Cycloaddition of *N*-Glycosyl-*C*-dialkoxyphosphonoylnitrones

by **Andrea Vasella** and **Robert Voeffray**

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

(20.VIII.82)

Summary

Addition of dialkyl phosphites to the nitrone **6**, formed *in situ* from the oxime **5** and formaldehyde gave the hydroxylamines **7** (86%) and **8** (88%), which reacted with *p*-benzoquinone in the presence of ethylene *via* the *C*-dialkoxyphosphonoylnitrones **9** and **10** to yield the cycloaddition products **11**–**14** (80–85%) with a diastereoselectivity of about 50%. The cycloaddition products were transformed into the monoisopropylidene derivatives **15**–**18** and the diacetates **19**–**22**. Comparison of the NMR. spectra and the specific rotations of the compounds **19**–**22** with those of the corresponding α-amino-acid derivatives **23**–**26** of known configuration indicated preferential formation of the L-isomers. The cycloaddition products were transformed in good yield into the L-α-aminophosphonic acids **29**, **30**, **36**, and **39**.

Introduction. – α-Aminophosphonic acids, analogs of α-amino acids [1–3], have numerous applications, *e.g.*, complexing agents [4] [5], antibiotics [6–10], herbicides [11], insecticides [11], and enzyme inhibitors [12] [13]. In several cases, their activity has been shown to depend upon their absolute configuration [8–10] but few methods for the asymmetric synthesis of aminophosphonic acids have been described [14] [15]. We have reported briefly on the asymmetric synthesis of some amino acids [16] based upon a 1,3-dipolar cycloaddition of *N*-glycosyl-*C*-alkoxycarbonylnitrones such as **1** and wondered whether *N*-glycosyl-*C*-dialkoxyphosphonoylnitrones such as **2** could be used in an analogous way for the asymmetric synthesis of aminophosphonic acids. *C*-Phosphononitrones were, to our knowledge, unknown and their preparation from appropriate hydroxylamines and formylphosphonates appeared problematic considering the cleavage of the C,P-bond observed when alkoylphosphonates reacted with secondary amines [17]. Indeed, reaction of the oxime **5** [18] *(Scheme 1)* with a preparation of dimethyl formylphosphonate[1]) (**3**, $R = CH_3$) in the presence of ethylene as dipolarophile only gave 2,3:5,6-di-*O*-isopropylidene-mannose and the *N*, *N*-diglycosylated hydroxylamine **4**.

[1]) The preparation of dimethyl formylphosphonate **3** ($R = CH_3$) has been briefly reported in a patent [19]. Following the indications we obtained what appears to be a mixture containing the desired compound and presumably oligomers thereof.

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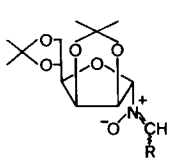
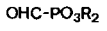


1 $R = CO_2R^1$
2 $R = PO_3R_2^1$



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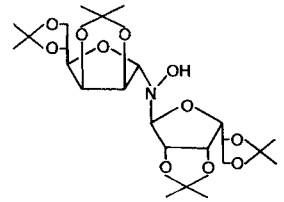

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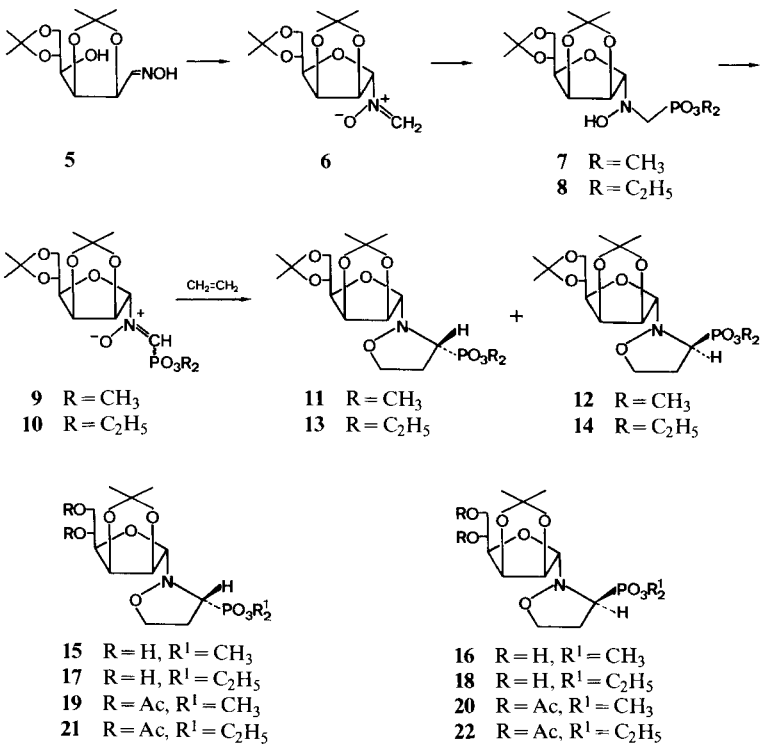
Synthesis. – Nitrones react with a variety of nucleophiles to give *N,N*-disubstituted hydroxylamines [21] [22] and these hydroxylamines can be oxidized in several ways to nitrones [23]. This indicates a way to *C*-phosphononitrones. In fact, reaction of dimethyl or diethyl phosphite with the nitrone **6** formed *in situ* from the oxime **5** and formaldehyde gave the (*N*-glycosyl)hydroxylaminophosphonate **7** and **8** in yields of 86 and 88% *(Scheme 1)*[2]).

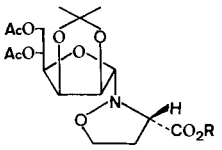
Scheme 1



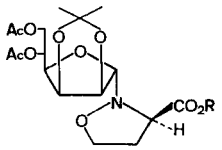
5 **6**
7 $R = CH_3$
8 $R = C_2H_5$
9 $R = CH_3$
10 $R = C_2H_5$
11 $R = CH_3$
13 $R = C_2H_5$
12 $R = CH_3$
14 $R = C_2H_5$
15 $R = H, R^1 = CH_3$
17 $R = H, R^1 = C_2H_5$
19 $R = Ac, R^1 = CH_3$
21 $R = Ac, R^1 = C_2H_5$
16 $R = H, R^1 = CH_3$
18 $R = H, R^1 = C_2H_5$
20 $R = Ac, R^1 = CH_3$
22 $R = Ac, R^1 = C_2H_5$

$Z = OCOCH_2Ph$

[2]) It is not clear if these compounds are formed by nucleophilic addition (non-concerted process) or by 1,3-dipolar addition to the P,H-bond (concerted process).



23 R = *t*-Bu
25 R = CH_2Ph



24 R = *t*-Bu
26 R = CH_2Ph

Oxidation of the hydroxylamine **7** with *p*-benzoquinone in the presence of ethylene (70–75°, 50 bar, autoclave) gave the cycloaddition products **11** and **12** (81%) in a ratio of 3:1 (^{1}H-NMR.). These isomers could not be separated by chromatography, but separation of the corresponding monoisopropylidene derivatives **15** and **16** (70% from **5**) obtained by partial deprotection posed no problem. The monoisopropylidene derivatives **15** and **16** were further characterized as the diacetates **19** and **20**. The ethyl esters **13**, **14**, **17**, **18**, **21**, and **22** were obtained in an analogous way from the hydroxylaminophosphonate **8**. The ^{1}H-NMR. spectra showed that all the cycloaddition products are of *α*-D-configuration, as indicated by the low $J(1',2')$ of about 0 Hz.

Since the ^{1}H-NMR. spectra of the diacetates **19** to **22** were particularly well-resolved, they were compared with those of the corresponding carboxylates **23** to **26** [24]. All these compounds possess very similar conformations judging by the similarity of the coupling constants. However, the chemical shifts in the ^{1}H- and ^{13}C-NMR. spectra of corresponding pairs of compounds epimeric at C(3) were distinctly different and only weakly influenced by the nature of the ester alkoxy groups (see *Tables 1* and *2*). The similarity of the chemical shifts of the major isomers of the phosphonates with those of the major isomers of the corresponding carboxylates for which the L-configuration has been proven [16] [24] strongly

Table 1. *Chemical shifts in the ^{1}H-NMR. spectra of the* N-*glycosylisoxazolidinephosphonates* **19** *to* **22** *and the analogous carboxylates* **23** *to* **26**

	Phosphonates major isomers		Carboxylates major isomers (L-configuration [24])		Phosphonates minor isomers		Carboxylates minor isomers (D-configuration [24])	
	19	**21**	**23**	**25**	**20**	**22**	**24**	**26**
H–C(1′)	4.32	4.31	4.37	4.39	4.90	4.93	4.88	4.88
H–C(2′)	4.93	4.93	4.97	4.97	5.02	5.03	5.01	5.02
H–C(3′)	4.77	4.75	4.77	4.77	4.77	4.79	4.75	4.75
H–C(4′)	4.39	4.37	4.34	4.32	4.30	4.30	4.31	4.29
H–C(5′)	5.26	5.27	5.29	5.25	5.17	5.18	5.16	5.16
H–C(6′)	4.21	4.19	4.14	4.08	4.18	4.23	4.19	4.19
H–C(6′)	4.52	4.48	4.51	4.47	4.56	4.56	4.55	4.55
H–C(3)	3.84	3.81	3.91	4.05	3.73	3.86	3.85	3.90
H–C(4)	2.39	2.41	2.43	2.52	2.49	2.45	2.40	2.46
H–C(4)	2.60	2.51	2.44	2.53	2.58	2.52	2.41	2.47
H–C(5)	3.98	3.96	3.97	4.00	3.77	3.69	3.87	3.89
H–C(5)	3.98	3.97	3.97	4.00	3.85	3.80	3.92	4.06

Table 2. *Chemical shifts in the ^{13}C-NMR. spectra of the* N-*glycosylisoxazolidinephosphonates* **19** *to* **22** *and the analogous carboxylates* **23** *to* **26**

	Phosphonates major isomers		Carboxylates major isomers (L)		Phosphonates minor isomers		Carboxylates minor isomers (D)	
	19	**21**	**23**	**25**	**20**	**22**	**24**	**26**
C(1′)	95.63	95.49	96.53	96.50	98.74	98.81	98.51	98.64
C(2′)	83.82	83.87	83.63	83.71	84.85	84.85	84.22	84.16
C(3′)[a]	79.67	79.57	79.91	79.64	80.38	80.34	80.31	80.28
C(4′)[a]	79.76	79.92	80.10	79.98	81.62	81.53	81.55	81.58
C(5′)	69.14	69.08	69.10	68.97	69.56	69.55	69.54	69.48
C(6′)	63.14	63.11	63.14	63.09	63.25	63.28	63.43	63.28
C(3)	55.95	56.14	63.14	62.58	53.02	55.20	61.52	61.11
C(4)	29.41	29.40	31.39	31.43	32.52	32.69	33.50	33.46
C(5)	66.31	66.40	66.63	66.58	67.08	67.03	67.26	67.39

[a]) Assignments may be reserved [25].

indicates the same configuration for the analogous phosphonates[3]). This conclusion is corroborated by the comparison of the specific rotations (see *Table 3*).

It thus appears that *C*-dialkoxyphosphonoylnitrones and *C*-alkoxycarbonylnitrones behave very similarly. To prove the usefulness of the former for the asymmetric synthesis of aminophosphonic acids, the cycloaddition products **15** and **17** were transformed into the free aminophosphonic acids **29**, **30**, **36**, and **39**, analogs of L-5-oxaproline [16], L-homoserine, L-aspartic acid, and L-asparagine *(Scheme 2)*.

Glycoside cleavage of the dimethyl ester **15** followed by benzyloxycarbonylation gave the fully protected aminophosphonate **28** (72%)[4]), which was directly transformed into the free aminophosphonic acid **29** (87%)[5]) by treatment with hydrobromic acid in acetic acid. Hydrogenolysis of **29** gave the homoserine analog **30** (95%). In order to prepare the aminophosphonic-acid analogs of aspartic acid and asparagine, we hydrogenolyzed the dimethyl ester **27**, but the product was unstable and attempted *N*-acylations failed. The diethyl ester **31**, however, obtained from **17** (87%) was hydrogenolyzed and benzyloxycarbonylated to give the protected

Table 3. *Specific rotations of the* N-*glycosylisoxazolidinecarboxylates* **23** *to* **26** *and the analogous phosphonates* **19** *to* **22** ($c = 1$, $CHCl_3$)

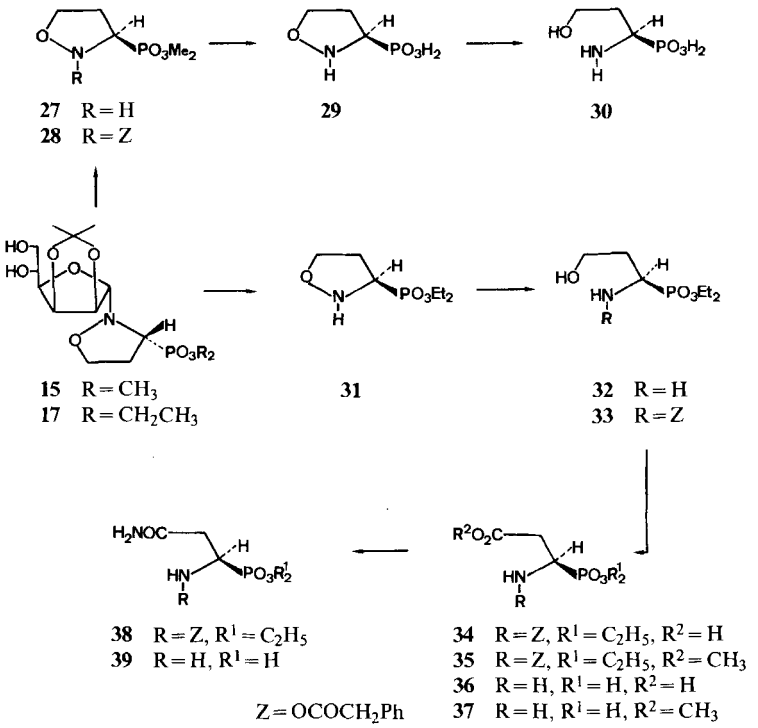
Carboxylates major isomers (L)		Phosphonates major isomers		Carboxylates minor isomers (D)		Phosphonates minor isomers	
23	**25**	**19**	**21**	**24**	**26**	**20**	**22**
−19.3	−18.3	−5.6	−10.5	+102.9	+91.2	+78.2	+89.4

[3]) By analogy with the synthesis of D-amino acids [16], the enantiomeric aminophosphonic acids should be available from *N*-ribosylnitrones.

[4]) This compound and the corresponding methyl L-carboxylate [16] possess very similar specific rotations ($[\alpha]_D = -83.3°$ and $-97.8°$, respectively).

[5]) This acid is much more stable than the analogous carboxylic acid which decomposes readily [16] [24].

Scheme 2



analog of homoserine **33** (86%) *(Scheme 2)*. This compound was oxidized with permanganate to the partially protected analog of aspartic acid **34**, which was characterized as the methyl ester **35**. Both **34** and **35** were treated with hydrobromic acid in acetic acid yielding the aminophosphonic acid **36** (90%) and the methyl ester **37** (62%), respectively. On the other hand, the partially protected acid **39** was transformed into the analog of asparagine by acid treatment of the amide **38**, obtained by ammonolysis of the mixed anhydride formed from **34** and isobutoxycarbonyl chloride.

Financial support of this work by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung* and *Sandoz* Ltd., Basel, is gratefully acknowledged. We thank Mrs. *A. Lorenzi* for the MS. spectra. Mr. *Pang-Chin Chen* and Mr. *R. Kunz* for the NMR. spectra and Mr. *H. Frohofer* for the microanalysis.

Experimental Part

General remarks. After extraction, the organic phases were dried ($MgSO_4$) and concentrated in a rotary evaporator below 40°. Thin layer chromatography (TLC.) was effected on 0.25 mm precoated silica gel plates (Kieselgel *60 F_{254}, Merck*). They were developed with an acidic iodine solution and/or an alcoholic ninhydrine solution. Column chromatography was performed on silica gel (Kieselgel *60*,

Merck), 70-230 mesh, or 230–400 mesh, for rapid chromatography [26] or chromatography according to *Loibner & Seidl* (LSC.) [27]. The following solvent mixtures were used: A: ethyl acetate/hexane 2:1; B: $CHCl_3/CH_3OH$ 9:1; C: CH_2Cl_2/CH_3OH 9:1; D: CH_2Cl_2/CH_3OH 19:1; E: ethyl acetate/hexane/CH_3OH 20:4:1. Melting points (m.p.) were determined on a *Büchi-SMP-20* apparatus and are uncorrected. Specific rotations ($[\alpha]_D$) were measured on a *Perkin-Elmer Spectrophotometer 241* at 25° using a 1-dm-cell at 365, 436, 546, 578, and 589 nm and extrapolated for 589 nm. – IR. spectra were run on a *Perkin-Elmer 298* spectrophotometer. Absorptions are given in cm^{-1} (*s* strong, *m* medium, *w* weak). – ^{1}H-NMR.-spectra (frequency, solvent) were measured on a *Varian EM-390* (90 MHz) or on a *Varian XL-200* (200 MHz) spectrometer and ^{13}C-NMR.-spectra (solvent) on a *Varian XL-100-12 FT* at 25.2 MHz. The chemical shifts are reported in (ppm) relative to TMS as internal reference or external reference when D_2O was the solvent. In these cases, the products were first freeze-dried twice with D_2O. Multiplicities (*s* singulet, *d* doublet, *t* triplet, *qa* quadruplet, *m* multiplet), coupling constants *J* in Hz, relative intensities and assignments are given in parenthesis. Mass spectra (MS.) were registered on a *Varian 112S* mass spectrometer, peaks are reported in *m/z*-values and relative intensities in % of the base peak in parenthesis.

Dimethyl formylphosphonate (**3**, R = Me). To a suspension of 6.3 g (200 mmol) of NaH in 140 ml of dry ether were added dropwise at −10°, over 30 min, 20 ml (210 mmol) of dimethyl phosphite. The suspension, which turned from grey to white during this addition, was stirred for further 2.5 h between −10° and +20°. After cooling to −10°, 19 g (200 mmol) of formic acetic anhydride were added dropwise leading to the formation of a white precipitate. The mixture was stirred for 3¼ h at −10° to +20° and centrifuged. The solid was washed with ether, the solvent evaporated and the residue distilled bulb-to-bulb giving 3.8 g (55–60°/15 Torr) of a fraction composed of dimethyl phosphite and formic acetic anhydride; 2.7 g (65–70°/0.03 Torr) of a mixture of non-characterized products and 13.1 g (47%, 165–170°/0.03 Torr) of **3** (R = Me). – IR. ($CHCl_3$): 3660*w*, 3455*w*, 2990*s*, 2950*s*, 2905*w*, 2850*m*, 2455*w*, 1760*s*, 1620*w*, 1455*m*, 1445*m*, 1367*m*, 1270*s*, 1145*s*, 975*w*. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 2.17 (*m*, 1 H); 3.50–4.00 (*m*, 6 H); 5.68 (*t*, *J* = 18, 1 H).

N,N-*Bis(2,3:5,6-di*-O-*isopropylidene-α*-D-*mannofuranosyl)hydroxylamine* (**4**). A solution of 1.5 g (5.45 mmol) of **5** and 1.2 g (8.5 mmol) of **3** (R = Me) in 15 ml of $CHCl_3$ was stirred in an autoclave, under 50 atm of ethylene, for 22 h at 70–75° (bath temp.). The solution was concentrated and the residue chromatographed on 120 g of silica gel (A) yielding 320 mg (22%) of 2,3:5,6-di-*O*-isopropylidene-*α*-D-mannofuranose and 950 mg (67%) of **4**, Rf(A) 0.31; $[\alpha]_D^{25} = +31.8$ (*c* = 1, $CHCl_3$). – IR. ($CHCl_3$): 3560*w*, 3360*w*, 2990*s*, 2940*m*, 2890*w*, 1455*w*, 1382*s*, 1372*s*, 1260*m*, 1215*m*, 1070*s*, 975*w*, 947*w*, 890*w*, 860*m*, 840*m*. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 1.34 (*s*, 6 H); 1.42 (*s*, 3 H); 1.47 (*s*, 3 H); 4.00–4.45 (*m*, 4 H); 4.77 (*d*×*d*, *J* = 6 and 3, 1 H, H–C(3)); 4.83 (*s*, 1 H, H–C(1)); 4.97 (*d*, *J* = 6, 1 H, H–C(2)); 5.82 (*s*, 1 H, exchangeable with D_2O, OH). – ^{13}C-NMR. ($CDCl_3$): 112.43 (*s*); 108.93 (*s*); 97.23 (*d*); 83.65 (*d*); 83.59 (*d*); 80.47 (*d*); 73.69 (*d*); 66.54 (*t*); 26.82 (*qa*); 26.12 (*qa*); 25.15 (*qa*); 24.58 (*qa*). – MS.: 517 (0.5, M^+), 503 (1), 502 (5), 459 (5), 246 (5), 185 (76), 167 (8), 143 (9), 141 (15), 127 (56), 101 (51), 99 (33), 98 (18), 85 (38), 72 (14), 71 (18), 69 (26), 68 (14), 59 (52), 57 (16), 43 (100).

$C_{24}H_{39}NO_{11}$ (517.58) Calc. C 55.70 H 7.59 N 2.72% Found C 55.84 H 7.39 N 2.91%

Dimethyl N-*(2,3:5,6-di*-O-*isopropylidene-α*-D-*mannofuranosyl)hydroxylaminomethylphosphonate* (**7**). To a solution of 5.5 g (20 mmol) of **5** in 100 ml of THF was added 1.2 g (40 mmol) of paraformaldehyde and the suspension was stirred for 1 h at r.t. After heating to 60°, 4 ml (33.6 mmol) of dimethyl phosphite in 200 ml THF were added dropwise over 6 h. The mixture was stirred for a further 18 h at 60° and the solvent evaporated. Rapid chromatography of the residue on 250 g of silica gel (A, then C) yielded 6.8 g (86%) of 7. Rf(B) 0.53, $[\alpha]_D^{25} = +13.5$ (*c* = 1, $CHCl_3$). – IR. ($CHCl_3$): 3670*w*, 3560*w*, 3280*w*, 2995*m*, 2960*m*, 2900*w*, 2860*w*, 1603*w*, 1455*w*, 1385*m*, 1375*m*, 1162*m*, 1065*s*, 1040*s*, 975*w*, 952*w*, 910*m*, 890*w*, 860*w*, 845*m*. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 1.33 (*s*, 3 H); 1.35 (*s*, 3 H); 1.43 (*s*, 3 H); 1.47 (*s*, 3 H); 3.11 (*d*×*d*, *J* = 15.5 and 13, 1 H); 3.51 (*d*×*d*, *J* = 15.5 and 10, 1 H); 3.79 (*d*, *J* = 11, 6 H); 4.00–4.45 (*m*, 4 H); 4.55 (*s*, 1 H, H–C(1)); 4.82 (*d*×*d*, *J* = 6 and 3.4, 1 H, H–C(3)); 5.04 (*d*, *J* = 6, 1 H, H–C(2)); 7.51 (*s*, 1 H, exchangeable with D_2O, OH). – ^{13}C-NMR. ($CDCl_3$): 112.07 (*s*); 108.89 (*s*); 100.36 (*d*×*d*, *J*(P,C) = 18); 84.32 (*d*); 83.92 (*d*); 80.57 (*d*); 73.67 (*d*); 66.68 (*t*); 52.71 (*qa*×*d*, *J*(P,C) = 6.5); 50.29 (*t*×*d*, *J*(P,C) = 170); 26.79 (*qa*); 25.97 (*qa*); 25.19 (*qa*); 24.34 (*qa*).

Diethyl N-*(2,3:5,6-di*-O-*isopropylidene-α*-D-*mannofuranosyl)hydroxylaminomethylphosphonate* (**8**). The same procedure as for the preparation of **7**, using 1.6 g (5.8 mmol) of **5**, 380 mg (12.7 mmol) of

paraformaldehyde and 1.45 ml (10.3 mmol) of diethyl phosphite gave, after chromatography (LSC.) on 220 g of silica gel (E) 2.18 g (88%) of **8**. An analytical sample was prepared by distillation *i.v.*: b.p. *115–120°/10*$^{-4}$ Torr. *Rf(D) 0.50*, $[\alpha]_D^{25} = +18.4$ (*c* = 1, $CHCl_3$). – *IR.* ($CHCl_3$): *3760w, 3555w, 3350w, 2990s, 2940m, 2910m, 1475w, 1455w, 1442w, 1380m, 1370m, 1160m, 1055s, 1030s, 978s, 885w, 860w, 840m.* – ^{1}H-NMR. (200 MHz, $CDCl_3$): 1.31 (*s*, 3 H); 1.32 (*t*, *J* = 7, 3 H); 1.36 (*s*, 3 H); 1.36 (*t*, *J* = 7, 3 H); 1.41 (*s*, 3 H); 1.45 (*s*, 3 H); 3.04 (*d*×*d*, *J* = 15 and 14); 3.43 (*d*×*d*, *J* = 15 and 8); 4.00–4.25 (*m*, 6 H); 4.28 (*m*, 2 H, H–C(6)); 4.53 (*s*, 1 H, H–C(1)); 4.82 (*d*×*d*, *J* = 6 and 4, 1 H, H–C(3)); 5.01 (*d*, *J* = 6, 1 H, H–C(2)); 7.85 (*s*, exchangeable with D_2O, OH). – ^{13}C-NMR. ($CDCl_3$): 111.95 (*s*); 108.87 (*s*); 100.21 (*d*×*d*, *J*(P,C) = 17.5); 84.42 (*d*); 84.04 (*d*); 80.65 (*d*); 73.72 (*d*); 66.80 (*t*); 62.18 (*t*×*d*, *J*(P,C) = 6.5); 61.69 (*t*×*d*, *J*(P,C) = 6); 51.10 (*t*×*d*, *J*(P,C) = 170); 26.81 (*qa*); 26.10 (*qa*); 25.25 (*qa*); 24.37 (*qa*); 16.41 (*qa*×*d*, *J*(P,C) = 6); 16.31 (*qa*×*d*, *J*(P,C) = 6).

$C_{17}H_{32}NO_9P$	Calc.	C 48.00	H 7.58	N 3.29	P 7.28%
(425.42)	Found	„ 48.37	„ 7.82	„ 3.50	„ 7.01%

*Dimethyl (3*R*)- and (3*S*)-2-(2,3:5,6-di-*O*-isopropylidene-α-*D*-mannufuranosyl)isoxazolidine-3-phosphonate* ((**11**) and (**12**)). In an autoclave, a mixture of 1 g (2.52 mmol) of **7**, 870 mg (8 mmol) of *p*-benzoquinone and 20 ml of $CHCl_3$ was stirred for 1 h at r.t. The autoclave was closed, pressurized to 50 atm with ethylene and heated for 16 h at 70–75° (bath temp.). The resulting mixture was dissolved in 60 ml of CH_2Cl_2 and 30 ml of 10% aq. NaOH-solution and extracted with of CH_2Cl_2 (3 × 60 ml). The organic phases were washed once with 20 ml of 10% aq. NaOH-solution, once with 15 ml of a sat. NaCl-solution, dried and evaporated *i.v.* Rapid chromatography of the residue on 100 g of silica gel (E) gave 865 mg (81%) of **11** and **12** (^{1}H-NMR.), 3:1-mixture by integration of the peaks at 4.23 (H–C(4′)), 4.34 (H–C(1′)), 4.40 (H–C(5′)), 4.85 (H–C(3′)), and 5.03 (H–C(2′)) for the major isomer, and at 4.16 (H–C(4′)), 4.36 (H–C(5′)), 4.85 (H–C(3′)), 4.90 (H–C(1′)), and 6.05 (H–C(2′)) for the minor isomer. Chromatography (LSC., E) of this material gave the mixture and a small amount of pure **11**.

Data of **11**. Rf(B) 0.74, $[\alpha]_D^{25} = -7.0$ (*c* = 1, $CHCl_3$). – IR. ($CHCl_3$): 3000*m*, 2960*m*, 2900*w*, 1860*w*, 1435*m*, 1385*m*, 1375*m*, 1160*m*, 1120*m*, 1095*s*, 1065*s*, 1040*s*, 970*w*, 950*w*, 910*w*, 885*w*, 840*w*. – ^{1}H-NMR. (200 MHz, $CDCl_3$): 1.34 (*s*, 3 H); 1.37 (*s*, 3 H); 1.44 (*s*, 3 H); 1.48 (*s*, 3 H); 2.50 (*d*×*d*×*d*, *J* = 7.3, 7.3 and 7.3, 1 H, H–C(4)); 2.60 (*d*×*d*×*d*, *J* = 7.3, 7.3 and 7.3, 1 H, H–C(4)); 3.83 (*d*, *J* = 10.5, 3 H); 3.84 (*d*, *J* = 10.5, 3 H); 3.88 (*d*×*d*, *J* = 7.3 and 7.3, 1 H, H–C(5)); 3.96 (*d*×*d*, *J* = 7.3 and 7.3, 1 H, H–C(5)); 4.02 (*d*×*d*×*d*, *J* = 10.5, 7.3 and 7.3, 1 H, H–C(3)); 4.09 (*d*, *J* = 4.8, 2 H, H–C(6′)); 4.23 (*d*×*d*, *J* = 7.5 and 3.6, 1 H, H–C(4′)); 4.34 (*d*, *J* = 1.2, 1 H, H–C(1′)); 4.40 (*d*×*d*×*d*, *J* = 7.5, 4.8 and 4.8, 1 H, H–C(5′)); 4.85 (*d*×*d*, *J* = 6 and 3.6, 1 H, H–C(3′)); 5.03 (*d*, *J* = 6, 1 H, H–C(2′)). – ^{13}C-NMR. ($CDCl_3$): 112.31 (*s*); 109.01 (*s*); 96.03 (*d*×*d*, *J*(P,C) = 15); 83.88 (*d*); 81.95 (*d*); 80.11 (*d*); 73.00 (*d*); 66.52 (*t*); 66.30 (*t*×*d*, *J*(P,C) = 2); 55.99 (*d*×*d*, *J*(P,C) = 180); 53.71 (*qa*×*d*, *J*(P,C) = 6.5); 52.98 (*qa*×*d*, *J*(P,C) = 6.5); 29.55 (*t*×*d*, *J*(P,C) = 1); 26.94 (*qa*); 25.92 (*qa*); 25.14 (*qa*); 24.50 (*qa*).

Data of **12**. Rf(B) 0.74. – ^{1}H-NMR. (200 MHz, $CDCl_3$): 1.34 (*s*, 3 H); 1.37 (*s*, 3 H); 1.44 (*s*, 3 H); 1.49 (*s*, 3 H); 2.50 (*d*×*d*×*d*, *J* = 7.3, 7.3 and 7.3, 1 H, H–C(4)); 2.60 (*d*×*d*×*d*, *J* = 7.3, 7.3 and 7.3, 1 H, H–C(4)); 3.84 (*d*, *J* = 10.5, 6 H); 3.80–4.15 (*m*, 5 H); 4.16 (*d*×*d*, *J* = 7 and 3.6, 1 H, H–C(4′)); 4.36 (*d*×*d*×*d*, *J* = 7, 5 and 5, 1 H, H–C(5′)); 4.85 (*d*×*d*, *J* = 6 and 3.6, 1 H, H–C(3′)); 4.90 (*s*, 1 H, H–C(1′)); 5.06 (*d*, *J* = 6, 1 H, H–C(2′)).

*Diethyl (3*R*)- and (3*S*)-2-(2,3:5,5-di-*O*-isopropylidene-α-*D*-mannofuranosyl)isoxazolidine-3-phosphonate* ((**13**) and (**14**)). As described for the preparation of **11** and **12**, 1 g (2.35 mmol) of **8** and 900 g (8.3 mmol) of *p*-benzoquinone gave 850 mg (80%) of **13** and **14** (^{1}H-NMR.), 3:1-mixture by integration of the peaks at 4.32 (H–C(1′)), 4.84 (H–C(23′)), and 5.01 (H–C(2′)) for the major isomer and at 4.84 (H–C(3′)), 4.92 (H–C(1′)), and 5.06 (H–C(2′)) for the minor isomer.

Data of **13**. Rf(B) 0.74. – ^{1}H-NMR. (200 MHz, $CDCl_3$): 1.34 (*s*, 3 H); 1.34 (*t*, *J* = 7.5); 1.38 (*s*, 3 H); 1.38 (*t*, *J* = 7.5); 1.43 (*s*, 3 H); 1.47 (*s*, 3 H); 2.48 (*d*×*d*×*d*, *J* = 7, 7 and 7, 1 H, H–C(4)); 2.58 (*d*×*d*×*d*, *J* = 7, 7 and 7, 1 H, H–C(4)); 3.70–4.25 (*m*, 10 H); 4.32 (*s*, 1 H, H–C(1′)); 4.38 (*d*×*d*×*d*, *J* = 8, 6 and 6, 1 H, H–C(5′)); 4.84 (*d*×*d*, *J* = 6 and 3.6, 1 H, H–C(3′)); 5.01 (*d*, *J* = 6, 1 H, H–C(2′)).

Data of **14**. Rf(B) 0.74. – ^{1}H-NMR. (200 MHz, $CDCl_3$): 1.34 (*s*, 3 H); 1.34 (*t*, *J* = 7.5); 1.38 (*s*, 3 H); 1.38 (*t*, *J* = 7.5); 1.43 (*s*, 3 H); 1.47 (*s*, 3 H); 2.48 (*d*×*d*×*d*, *J* = 7, 7 and 7, 1 H, H–C(4)); 2.58 (*d*×*d*×*d*, *J* = 7, 7 and 7, 1 H, H–C(4)); 3.65–4.30 (*m*, 11 H); 4.84 (*d*×*d*, *J* = 6 and 3.6, 1 H, H–C(3′)); 4,92 (*s*, 1 H, H–C(1′)); 5.06 (*d*, *J* = 6, H–C(2′)).

Dimethyl (3R)- and (3S)-2-(2,3-O-isopropylidene-α-D-mannofuranosyl)isoxazolidine-3-phosphonate ((**15**) and (**16**)). To a solution of 10 g (36.3 mmol) of the oxime **5** in 180 ml of THF were added 2.2 g (73 mmol) of paraformaldehyde and the suspension was stirred for 1 h at r.t. After heating to 60°, 8 ml (67.2 mmol) of dimethyl phosphite in 320 ml of THF were added dropwise over 6 h and the mixture stirred for 19 h at 60° and the solvent evaporated. Rapid chromatography of the residue on 250 g of silica gel (A, then C) gave 19.5 g (136%) of a mixture of **7** and dimethyl phosphite. This mixture was dried for 4 days in high vacuum and then dissolved in 20 ml $CHCl_3$ in an autoclave. To this solution were added 15 g (135 mmol) of 1,4-benzoquinone and the mixture was stirred for 1 h at r.t. The autoclave was pressurized to 50 atm with ethylene and then heated for 15 h at 70–75° (bath temp.). The product was extracted as described above. Evaporation of CH_2Cl_2 gave 12.8 g of a red syrup. It was dissolved in 180 ml of CH_3OH containing 18 ml of 36% aq. HCl-solution and stirred for 12 min at r.t., cooled to 0° and then neutralized with *Dowex* 1×4 (50–100 mesh, OH^-). The resin was filtered off, the filtrate evaporated to dryness *i.v.* and the residue purified by chromatography (LSC.) on 1.1 kg of silica gel (D, then C) yielding 6.8 g (49% from **5**) of **15**, Rf(B) 0.44, and 2.95 g (21% from **5**) of **16**, Rf(B) 0.35. For analysis, a solution of 270 mg (0.7 mmol) of **15** in 4 ml pyridine and 2 ml acetic anhydride was kept for 2 h at r.t., concentrated *i.v.* and the residue purified by chromatography on 30 g of silica gel (CH_2Cl_2/CH_3OH 97:3) giving 309 mg (94%) of **19**. In a similar way, 280 mg of **16** gave 314 mg (93%) of **20**.

Data of dimethyl (3R)-2-(5,6-di-O-acetyl-2,3-O-isopropylidene-α-D-mannofuranosyl)isoxoazolidine-3-phosphonate (**19**). Rf(B) 0.62, $[\alpha]_D^{25} = -5.6$ ($c = 1$, $CHCl_3$). – IR. ($CHCl_3$): 3000*m*, 2960*m*, 2900*w*, 2860*w*, 1745*s*, 1460*w*, 1387*m*, 1375*s*, 1165*m*, 1125*m*, 1100*s*, 1065*s*, 1040*s*, 980*w*, 950*w*, 910*w*, 885*w*, 835*w*. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 1.30 (*s*, 3 H); 1.43 (*s*, 3 H); 2.05 (*s*, 3 H); 2.07 (*s*, 3 H); 2.39 (*d*×*d*×*d*, $J = 7.2$, 7.2 and 7.2, 1 H, H–C(4)); 2.60 (*d*×*d*×*d*, $J = 7.2$, 7.2 and 7.2, 1 H, H–C(4)); 3.79 (*d*, $J = 10.5$, 6 H); 3.84 (*d*×*d*×*d*, $J = 11$, 7.2 and 7.2, 1 H, H–C(3)); 3.98 (*d*×*d*, $J = 7.2$ and 7.2, 2 H, H–C(5)); 4.21 (*d*×*d*, $J = 12.5$ and 5.7, 1 H, couples with H–C(5′), 1 H, H–C(6′)); 4,32 (*d*, $J = 1$, 1 H, H–C(1′)); 4.39 (*d*×*d*, $J = 8$ and 3.6, couples with H–C(5′), 1 H, H–C(4′)); 4.53 (*d*×*d*, $J = 12.5$ and 2.4, couples with H–C(5′), 1 H, H–C(6′)); 4.77 (*d*×*d*, $J = 6$ and 3.6, 1 H, H–C(3′)); 4.93 (*d*, $J = 6$, 1 H, H–C(2′)); 5.26 (*d*×*d*×*d*, $J = 8$, 5.7 and 2.4, 1 H, H–C(5′)). – ^{13}C-NMR. ($CDCl_3$): 170.53 (*s*); 169.36 (*s*); 112.55 (*s*); 95.63 (*d*×*d*, $J(P,C) = 15$); 83.82 (*d*); 79.96 (*d*); 79.67 (*d*); 69.14 (*d*); 66.31 (*t*×*d*, $J(P,C) = 1.5$); 63.14 (*t*); 55.95 (*d*×*d*, $J(P,C) = 180$); 53.24 (*qa*×*d*, $J(P,C) = 6.5$); 53.14 (*qa*×*d*, $J(P,C) = 6.5$); 29.41 (*t*); 25.96 (*qa*); 24.76 (*qa*); 20.90 (*qa*); 20.70 (*qa*).

$C_{18}H_{30}NO_{11}P$	Calc.	C 46.25	H 6.47	N 3.00	P 6.63%
(467.41)	Found	„ 46.40	„ 6.58	„ 2.77	„ 6.40%

Data of dimethyl (3S)-2-(5,6-di-O-acetyl-2,3-O-isopropylidene-α-D-mannofuranosyl)isoxazolidine-3-phosphonate (**20**). Rf(B) 0.62, $[\alpha]_D^{25} = +78.2$ ($c = 1$, $CHCl_3$). – IR. ($CHCl_3$): 3000*m*, 2965*m*, 2880*w*, 2855*w*, 1745*s*, 1450*w*, 1385*m*, 1375*s*, 1160*w*, 1115*m*, 1060*s*, 1040*s*, 985*w*, 962*w*, 935*w*, 905*w*, 870*w*, 830*w*. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 1.30 (*s*, 3 H); 1.45 (*s*, 3 H); 2.03 (*s*, 6 H); 2.49 (*d*×*d*×*d*, $J = 7$, 7 and 7, 1 H, H–C(4)); 2.58 (*d*×*d*×*d*, $J = 7$, 7 and 7, H–C(4)); 3.73 (*d*×*d*×*d*, $J = 11$, 7 and 7, 1 H, H–C(3)); 3.77 (*d*×*d*, $J = 7$ and 7, 1 H, H–C(5)); 3.82 (*d*, $J = 10.5$, 6 H); 3.85 (*d*×*d*, $J = 7$ and 7, 1 H, H–C(5)); 4.18 (*d*×*d*, $J = 12.5$ and 4.8, couples with H–C(5′), 1 H, H–C(6′)); 4.30 (*d*×*d*, $J = 8.4$ and 4.2, couples with H–C(5′), 1 H, H–C(4′)); 4.56 (*d*×*d*, $J = 12.5$ and 2.4, couples with H–C(5′), 1 H, H–C(6′)); 4.77 (*d*×*d*, $J = 6$ and 4.2, 1 H, H–C(3′)); 4.90 (*s*, 1 H, H–C(1′)); 5.02 (*d*×*d*, $J = 6$ and 0.8, 1 H, H–C(2′)); 5.17 (*d*×*d*×*d*, $J = 8.4$, 4.8 and 2.4, 1 H, H–C(5′)). – ^{13}C-NMR. ($CDCl_3$): 170.20 (*s*); 169.21 (*s*); 112.53 (*s*); 98.74 (*d*×*d*, $J(P,C) = 8.8$); 84.25 (*d*); 81.62 (*d*); 80.38 (*d*); 69.56 (*d*); 67.08 (*t*×*d*, $J(P,C) = 7.6$); 63.25 (*t*); 55.03 (*d*×*d*, $J(P,C) = 175$); 53.53 (*qa*×*d*, $J(P,C) = 6.5$); 53.45 (*qa*×*d*, $J(P,C) = 6.5$); 32.59 (*t*×*d*, $J(P,C) = 2$); 26.11 (*qa*); 24.76 (*qa*); 20.84 (*qa*); 20.71 (*qa*).

$C_{18}H_{30}NO_{11}P$	Calc.	C 46.25	H 6.47	N 3.00	P 6.63%
(467.41)	Found	„ 46.35	„ 6.65	„ 2.90	„ 6.49%

Diethyl (3R)- and (3S)-2-(2,3-O-isopropylidene-α-D-mannofuranosyl)isoxazolidine-3-phosphonate ((**17**) and (**18**)). Similarly to the preparation of **15** and **16**, 7 g (25.2 mmol) of **5**, 1.5 g (49.7 mmol) of formaldehyde and 5.7 ml (47.9 mmol) of diethyl phosphite reacted together to give after rapid chromatography 9.85 g (91%) of **8** containing a trace of diethyl phosphite. This product was transformed into **17** and **18** and then partially deprotected as described above. The crude product was chromatographed

(LSC.) on 700 g of silica gel (D, then C) giving 4.35 g (42% from **5**) of **17**, Rf(D) = 0.25 and 2.05 g (20% from **5**) of **18**, Rf(D) 0.17. For analysis, 315 mg (0.76 mmol) of **17** were acetylated to give 370 mg (93%) of **21**, purified by rapid chromatography on 30 g of silica gel (D). Similarly, 270 mg (0.65 mmol) of **18** were acetylated to yield 302 mg (93%) of **22**. Analytical samples were prepared by distillation *i.v.*: b.p. = 105–110°/10^{-4} Torr.

*Data of diethyl (3*R*)-2-(5,6-di-*O*-acetyl-2,3-*O*-isopropylidene-α-*D*-mannofuranosyl)isoxazolidine-3-phosphonate* (**21**). Rf(D) 0.33, $[\alpha]_D^{25} = -10.5$ ($c = 1$, $CHCl_3$). – IR. ($CHCl_3$): 2990*m*, 2935*w*, 2905*w*, 2870*w*, 1742*s*, 1455*w*, 1445*w*, 1385*m*, 1375*s*, 1160*m*, 1132*m*, 1095*s*, 1070*s*, 1055*s*, 1030*s*, 970*s*, 910*m*, 880*w*, 870*w*. – ^{1}H-NMR. (200 MHz, $CDCl_3$): 1.27 (*s*, 3 H); 1.32 (*t*, $J = 7.5$, 3 H); 1.38 (*t*, $J = 7.5$, 3 H); 1.43 (*s*, 3 H); 2.03 (*s*, 3 H); 2.06 (*s*, 3 H); 2.41 (*d*×*d*×*d*, $J = 7$, 7 and 7, 1 H, H–C(4)); 2.51 (*d*×*d*×*d*, $J = 7$, 7 and 6, 1 H, H–C(4)); 3.81 (*d*×*d*×*d*, $J = 11$, 7 and 6, 1 H, H–C(3)); 3.96 (*d*×*d*, $J = 7$ and 7, 1 H, H–C(5)); 3.97 (*d*×*d*, $J = 7$ and 7, 1 H, H–C(5)); 4.12 (*qa*×*d*, $J = 7.5$ and 7.5, 2 H); 4.13 (*qa*×*d*, $J = 8$ and 7.5, 2 H); 4.19 (*d*×*d*, $J = 12$ and 6, 1 H, H–C(6′)); 4.31 (*s*, 1 H, H–C(1′)); 4.37 (*d*×*d*, $J = 8.5$ and 4, 1 H, H–C(4′)); 4.48 (*d*×*d*, $J = 12$ and 2.2, 1 H, H–C(6′)); 4.75 (*d*×*d*, $J = 6$ and 4, 1 H, H–C(3′)); 4.93 (*d*, $J = 6$, 1 H, H–C(2′)); 5.27 (*d*×*d*×*d*, $J = 8.5$, 6 and 2.2, 1 H, H–C(5′)). – ^{13}C-NMR. ($CDCl_3$): 170.52 (*s*); 169.31 (*s*); 112.48 (*s*); 95.49 (*d*×*d*, $J(P,C) = 15$); 83.87 (*d*); 79.92 (*d*); 79.57 (*d*); 69.08 (*d*); 66.40 (*t*×*d*, $J(P,C) = 1.5$); 63.11 (*t*); 62.54 (*t*×*d*, $J(P,C) = 6.5$); 62.46 (*t*×*d*, $J(P,C) = 6.5$); 56.14 (*d*×*d*, $J(P,C) = 180$); 29.40 (*t*); 25.97 (*qa*); 24.77 (*qa*); 20.88 (*qa*); 20.71 (*qa*); 16.52 (*qa*×*d*, $J(P,C) = 5.5$).

*Data of diethyl (3*S*)-2-(5,6-di-*O*-acetyl-2,3-*O*-isopropylidene-α-*D*-mannofuranosyl)isoxazolidine-3-phosphonate* (**22**). Rf(D) 0.33, $[\alpha]_D^{25} = +89.4$ ($c = 1$, $CHCl_3$). – IR. ($CHCl_3$): 2995*s*, 2940*w*, 2910*w*, 2880*w*, 1745*s*, 1465*w*, 1445*w*, 1385*m*, 1372*w*, 1162*m*, 1115*m*, 1095*s*, 1075*s*, 1050*s*, 1030*s*, 972*s*, 905*w*, 875*w*. – ^{1}H-NMR. (200 MHz, $CDCl_3$): 1.31 (*s*, 3 H); 1.34 (*t*, $J = 7.5$, 6 H); 1.44 (*s*, 3 H); 2.05 (*s*, 6 H); 2.45 (*d*×*d*×*d*×*d*, $J = 8$, 7, 7 and 3, 1 H, H–C(4)); 2.52 (*d*×*d*×*d*, $J = 8$, 7 and 7, 1 H, H–C(4)); 3.69 (*d*×*d*×*d*, $J = 8$, 8 and 2, 1 H, H–C(5)); 3.86 (*d*×*d*×*d*, $J = 14$, 7 and 7, 1 H, H–C(3)); 4.19 (*qa*×*d*, $J = 7.5$ and 7.5, 2 H); 4.20 (*qa*×*d*, $J = 7.5$ and 7.5, 2 H); 4.23 (*d*×*d*, $J = 12.5$ and 5.2, 1 H, H–C(6′)); 4.30 (*d*×*d*, $J = 8.5$ and 4.2, 1 H, H–C(4′)); 4.56 (*d*×*d*, $J = 12.5$ and 2.2, 1 H, H–C(6′)); 4.79 (*d*×*d*, $J = 6$ and 4.2, 1 H, H–C(3′)); 4.93 (*s*, 1 H, H–C(1′)); 5.03 (*d*, $J = 6$, 1 H, H–C(2′)); 5.18 (*d*×*d*×*d*, $J = 8.5$, 5.2 and 2.2, 1 H, H–C(5′)). – ^{13}C-NMR. ($CDCl_3$): 170.21 (*s*); 169.21 (*s*); 112.47 (*s*); 98.81 (*d*×*d*, $J(P,C) = 7$); 82.24 (*d*); 81.53 (*d*); 80.39 (*d*); 69.55 (*d*); 67.03 (*t*×*d*, $J(P,C) = 7$); 63.26 (*t*); 62.89 (*t*×*d*, $J(P,C) = 6.5$); 62.77 (*t*×*d*, $J(P,C) = 7$); 55.20 (*d*×*d*, $J(P,C) = 175$); 32.69 (*t*×*d*, $J(P,C) = 2$); 26.13 (*qa*); 24.83 (*qa*); 20.91 (*qa*); 20.72 (*qa*); 16.48 (*qa*×*d*, $J(P,C) = 5.5$).

$C_{20}H_{34}NO_{11}P$	Calc.	C 48.48	H 6.92	N 2.83	P 6.25%
(495.46)	Found	„ 48.18	„ 6.87	„ 2.61	„ 6.00%

*Diethyl (*R*)-isoxazolidine-3-phosphonate* (**31**). A solution of 1.1 g (26.7 mmol) of **17** in 12 ml of CH_3OH containing 1.2 ml of 36% aq. HCl was stirred for 3½ h at 40° and then neutralized with NaOAc. The major part of the CH_3OH was distilled off at 60°/50 Torr using a short *Vigreux* column. The residue was diluted with 15 ml of 0.5M Na_2CO_3 and extracted with CH_2Cl_2 (3×50 ml). The organic phases were dried and evaporated *i.v.* Rapid chromatography of the residue on 50 g of silica gel (E) gave 490 mg (82%) of **31**. An analytical sample was prepared by distillation *i.v.*: b.p. 60–65°/3 Torr. Rf(B) 0.51, $[\alpha]_D^{25} = +11.7$ ($c = 1$, $CHCl_3$). – IR. ($CHCl_3$): 3670*w*, 3420*w*, 3210*w*, 2995*s*, 2935*m*, 2910*m*, 2880*w*, 1475*w*, 1452*w*, 1445*w*, 1392*m*, 1370*w*, 1162*m*, 1100*m*, 1055*s*, 1030*s*, 970*s*, 848*w*. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 1.35 (*t*, $J = 7$, 6 H); 2.37 (*d*×*d*×*d*×*d*, $J = 8.2$, 7, 7 and 4, 1 H, H–C(4)); 2.53 (*d*×*d*×*d*, $J = 8$, 7 and 7, 1 H, H–C(4)); 3.54 (*d*×*d*×*d*, $J = 10$, 8.2 and 8, 1 H, H–C(3)); 3.89 (*d*×*d*, $J = 7$ and 7, 2 H, H–C(5)); 4.20 (*qa*×*d*, $J = 7$ and 7, 4 H); 5.20 (*s*, exchangeable with D_2O, NH). – ^{13}C-NMR. ($CDCl_3$): 69.84 (*t*×*d*, $J(P,C) = 6.5$); 62.65 (*t*×*d*, $J(P,C) = 6.5$); 62.55 (*t*×*d*, $J(P,C) = 7$); 55.88 (*d*×*d*, $J(P,C) = 160$); 31.95 (*t*); 16.44 (*qa*×*d*, $J(P,C) = 3.5$).

*Dimethyl (*R*)-2-benzyloxycarbonylisoxazoline-3-phosphonate* (**28**). A solution of 4.8 g (12.5 mmol) of **15** in 20 ml of CH_3OH containing 2 ml of 36% aq. HCl was stirred for 5 h at 40°, cooled to 0° and successively treated with 60 ml of 0.5M Na_2CO_3, 40 ml of $CHCl_3$ and 4 ml of benzyl chloroformate (90%, 25.3 mmol). The mixture was stirred vigorously for 5 h at r.t. The aqueous phase was neutralized with ice-cold 10% H_2SO_4-solution and the product extracted with CH_2Cl_2 (3×300 ml). The organic phases were washed with 80 ml of 0.5M Na_2CO_3, dried and evaporated *i.v.* Chromatography (LSC.) of the residue on 250 g of silica gel (C) gave 3.05 (72%) of **28**. An analytical sample was distilled *i.v.*: b.p. 115–120°/10^{-4} Torr. Rf(B) 0.57, $[\alpha]_D^{25} = -83.3$ ($c = 1$, $CHCl_3$). – IR. ($CHCl_3$): 3090*w*, 3060*w*,

3000*m*, 2955*m*, 2920*w*, 2880*w*, 2855*w*, 1720*s*, 1500*w*, 1455*m*, 1387*m*, 1320*m*, 1285*s*, 1180*m*, 1115*m*, 1055*s*, 1040*s*, 960*w*, 910*w*, 880*w*, 837*m*. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 2.48 ($d\times d\times d\times d$, J = 9, 8, 6.5 and 4.8, 1 H, H–C(4)); 2.57 ($d\times d\times d\times d$, J = 9, 8, 6.5 and 6, 1 H, H–C(4)); 3.59 ($d\times d\times d$, J = 8, 8 and 8, couples with H–C(5), 1 H, H–C(5)); 3.79 (*d*, J = 10.5, 6 H); 4.15 ($d\times d\times d$, J = 8, 6 and 4.8, 1 H, H–C(5)); 4.50 ($d\times d\times d$, J = 9, 6.5 and 6.5, 1 H, H–C(3)); 5.18 (*s*, 2 H); 7.36 (*s*, 5 H). – ^{13}C-NMR. ($CDCl_3$): 158.16 (*s*); 135.20 (*s*); 128.41 (*d*); 128.30 (*d*); 128.03 (*d*); 69.29 ($t\times d$, J(P,C) = 2); 68.60 (*t*); 54.32 ($d\times d$, J(P,C) = 177); 53.76 ($qa\times d$, J(P,C) = 6.5); 53.27 ($qa\times d$, J(P,C) = 6.5); 30.36 (*t*).

$C_{13}H_{18}NO_6P$	Calc.	C 49.53	H 5.76	N 4.44	P 9.82%
(315.26)	Found	„ 49.45	„ 5.97	„ 4.35	„ 9.66%

(R)-Isoxazolidine-3-phosphonic acid (**29**). A solution of 850 mg (2.7 mmol) of **28** in 20 ml of a 33% solution of HBr in acetic acid was stirred for 17 h at r.t. After evaporation of the solvents, the crude product was recrystallized from 3 ml of hot water and 8 ml of ethanol yielding 360 mg (87%) of **29**, Rf (pyridine/H_2O 2:1) 0.72, $[\alpha]_D^{25} = +30.8$ (c = 1, TFA). – IR. (KBr): 3430*m*, 3000–2000 (max), 1615*w*, 1448*m*, 1380*w*, 1310*w*, 1255*m*, 1232*s*, 1190*s*, 1170*s*, 1130*s*, 1080*s*, 1020*s*, 995*s*, 960*s*, 930*s*, 885*w*, 862*m*, 685*w*. – ^{1}H-NMR. (90 MHz, CF_3CO_2D): 2.70–3.20 (*m*, 2 H); 4.20–4.75 (*m*, 3 H); 9.87 (*s*, 1 H). – ^{13}C-NMR. (CF_3CO_2D): 73.06 ($t\times d$, J(P,C) = 7); 58.63 ($d\times d$, J(P,C) = 147); 30.78 (*t*).

$C_3H_8NO_4P$	Calc.	C 23.54	H 5.27	N 9.15	P 20.23%
(153.07)	Found	„ 23.51	„ 5.41	„ 9.01	„ 20.06%

Diethyl (R)-(1-benzyloxycarbonylamino-3-hydroxy-propyl)phosphonate (**33**). A solution of 3.5 g (8.51 mmol) of **17** in 50 ml of CH_3OH containing 5 ml of 36% aq. HCl was stirred for 3½ h at 40°. After neutralization with NaOAc (pH 7–8), the crude product containing **31** (Rf(B) 0.57) was treated with 300 mg 5% Rh/C and H_2 overnight. The catalyst was filtered off and washed with 20 ml of CH_3OH. The resulting filtrate containing **32** (Rf(B) 0.22) was concentrated to 8 ml and then diluted with 30 ml of $CHCl_3$. After the addition of 35 ml of M Na_2CO_3, 15 ml of M $NaHCO_3$ and 3 ml of benzyl chloroformate (90%, 19 mmol), the mixture was stirred vigorously for 5 h at r.t. The water phase was neutralized with ice-cold 10% aq. H_2SO_4-solution and the product extracted with CH_2Cl_2 (3 × 250 ml). The organic phases were washed with 80 ml of 0.5 M Na_2CO_3, dried and evaporated *i.v.* Chromatography (LSC.) of the residue on 250 g of silica gel (D) gave 2.37 g (80%) of **33**. An analytical sample was obtained by distillation *i.v.*: b.p. 105–110°/10^{-4} Torr. Rf(B) 0.45, $[\alpha]_D^{25} = -12.6$ (c = 1, $CHCl_3$). – IR. ($CHCl_3$): 3425*w*, 3000*s*, 2930*w*, 2910*w*, 1715*s*, 1505*m*, 1440*w*, 1390*m*, 1370*w*, 1320*w*, 1280*s*, 1162*m*, 1090*s*, 1035*s*, 970*s*. – ^{1}H-NMR. (200 MHz, $CDCl_3$): 1.27 (*t*, J = 7, 3 H); 1.31 (*t*, J = 7, 3 H); 1.72 (*m*, 1 H, H–C(2)); 2.07 (*m*, 1 H, H–C(2)); 2.45 (*s*, 1 H, exchangeable with D_2O, OH); 3.55–3.85 (*m*, 2 H, H–C(3)); 4.08 ($qa\times d$, J = 11 and 7, 2 H); 4.09 ($qa\times d$, J = 11 and 7, 2 H); 4.28 ($d\times d\times d\times d$, J = 15, 10, 6 and 4, 1 H, H–C(1)); 5.12 (*s*, 2 H); 5.33 (*d*, J = 10, 1 H, NH); 7.35 (*s*, 5 H). – ^{13}C-NMR. ($CDCl_3$): 156.65 (*d*, J(P,C) = 8); 136.11 (*s*); 128.29 (*d*); 127.98 (*d*); 127.84 (*d*); 67.11 (*t*); 62.87 ($t\times d$, J(P,C) = 7); 62.52 ($t\times d$, J(P,C) = 6.5); 58.10 ($t\times d$, J(P,C) = 13); 44.91 ($d\times d$, J(P,C) = 160); 32.77 ($t\times d$, J(P,C) = 3); 16.31 ($qa\times d$, J(P,C) = 5.5).

(R)-1-Amino-3-hydroxypropylphosphonic acid (**30**). A solution of 100 mg (6.64 mmol) of **29** in 10 ml water was treated with 40 mg 5% Rh/C and H_2 for 20 h. The mixture was filtered, the catalyst washed with 5 ml of water and the filtrate freeze-dried to give 96 mg (95%) of **30**, m.p. 214–217°. Rf (pyridin/H_2O 2:1) 0.44, $[\alpha]_D^{25} = -6.2$ (c = 1, H_2O). – IR. (KBr): 3500–1900 (max), 3420*m*, 3340*m*, 2955*m*, 2895*m*, 2420*s*, 2320*m*, 2200*s*, 2090*s*, 1465*w*, 1440*w*, 1380*w*, 1205*s*, 1190*s*, 1175*s*, 1160*s*, 1045*s*, 920*m*, 840*w*, 672*m*. – ^{1}H-NMR. (90 MHz, D_2O): 2.14 ($d\times d\times d\times d\times d$, J = 15, 9.5, 9, 6.3 and 6.3, 1 H, H–C(2)); 2.33 ($d\times d\times d\times d\times d$, J = 15, 9.5, 6.3, 6.3 and 5, 1 H, H–C(2)); 3.62 ($d\times d\times d$, J = 14, 9 and 5, 1 H, H–C(1)); 4.02 ($d\times d$, J = 6.3 and 6.3, 2 H, 2 H–C(3)). – ^{13}C-NMR. (D_2O): 59.83 ($t\times d$, J(P,C) = 10); 48.28 ($d\times d$, J(P,C) = 145); 31.33 (*t*).

Methyl (R)-3-benzyloxycarbonylamino-3-diethylphosphonopropionate (**35**). To a stirred solution of 650 mg (1.9 mmol) of **33** in 18 ml of acetone were added, over 30 min, 1.2 g of $KMnO_4$ and 9 ml of acetic acid, and the mixture was stirred for further 3½ h at r.t. The major part of the solvents was removed *i.v.*, the residue poured into 90 ml of 5% aq. H_2SO_4-solution containing 3 g of $NaHSO_3$ and the product extracted with CH_2Cl_2 (3 × 150 ml). The organic phases were extracted with 0.5 M Na_2CO_3 (3 × 100 ml). These extracts were neutralized with ice-cold 10% aq. H_2SO_4-solution and then reextracted with CH_2Cl_2 (4 × 100 ml). The organic phases were dried and concentrated *i.v.* To the solution of the

residue (580 mg) in 8 ml of $CHCl_3$ was added diazomethane in ether until the yellow color persisted. The solution was then decolored with acetic acid and concentrated *i.v.* Rapid chromatography on 50 g of silica gel (D) gave 520 mg (74% from **33**) of **35**. An analytical sample was distilled *i.v.*: b.p. 105–110°/ 10^{-4} Torr. Rf(D) 0.44, $[\alpha]_D^{25} = -6.7$ ($c = 1$, $CHCl_3$). – IR. ($CHCl_3$): 3430*m*, 3090*w*, 3060*w*, 3025*w*, 2997*s*, 2950*m*, 2910*w*, 2870*w*, 2850*w*, 1735*s*, 1725*s*, 1500*s*, 1453*m*, 1438*m*, 1392*w*, 1368*m*, 1305*s*, 1160*m*, 1140*w*, 1095*w*, 1040*s*, 1025*s*, 975*s*, 910*w*. – ^{1}H-NMR. (200 MHz, $CDCl_3$): 1.27 (*t*, $J = 7$, 3 H); 1.31 (*t*, $J = 7$, 3 H); 2.66 (*d*×*d*×*d*, $J = 15$, 8 and 8, 1 H, H–C(2)); 2.82 (*d*×*d*×*d*, $J = 15$, 14 and 5.5, 1 H, H–C(2)); 3.69 (*s*, 3 H); 4.12 (*qa*×*d*, $J = 9$ and 7, 2 H); 4.13 (*qa*×*d*, $J = 11$ and 7, 2 H); 4.55 (*d*×*d*×*d*×*d*, $J = 16$, 10, 8 and 5.5, 1 H, H–C(3)); 5.14 (*s*, 2 H); 5.42 (*d*, $J = 10$, 1 H, NH); 7.37 (*s*, 5 H). – ^{13}C-NMR. ($CDCl_3$): 170.29 (*d*, $J(P,C) = 14$); 155.47 (*d*, $J(P,C) = 1$); 136.16 (*s*); 128.27 (*d*); 127.92 (*d*); 67.03 (*t*); 62.99 (*t*×*d*, $J(P,C) = 7$); 62.65 (*t*×*d*, $J(P,C) = 7$); 51.92 (*qa*); 44.81 (*d*×*d*, $J(P,C) = 160$); 34.96 (*t*×*d*, $J(P,C) = 4.5$); 16.31 (*qa*×*d*, $J(P,C) = 4.5$); 16.29 (*qa*×*d*, $J(P,C) = 5.5$).

$C_{16}H_{24}NO_7P$	Calc.	C 51.47	H 6.48	N 3.75	P 8.30%
(373.34)	Found	,, 51.44	,, 6.50	,, 3.46	,, 8.15%

*Methyl (*R*)-3-amino-3-phosphonopropionate* (**37**). A solution of 305 mg (0.82 mmol) of **35** in 4 ml of a 33% solution of HBr in acetic acid was stirred for 17 h at r.t. After evaporation of the solvents, the crude product was recrystallized from 1 ml of hot water and 3 ml of ethanol yielding 96 mg (62%) of **37**. m.p. 156–160°, $[\alpha]_D^{25} = -26.6$ ($c = 1$, H_2O). – IR. (KBr): 3500–2000 (max), 3570*s*, 2820*s*, 2640*m*, 2560*m*, 2470*m*, 2115*w*, 1730*s*, 1640*m*, 1620*m*, 1530*s*, 1440*m*, 1405*w*, 1390*m*, 1260*s*, 1200*m*, 1180*s*, 1165*s*, 1120*s*, 1090*s*, 1062*s*, 1050*m*, 1000*w*, 935*s*, 895*w*, 880*w*, 768*w*. – ^{1}H-NMR. (90 MHz, D_2O): 2.95–3.30 (*m*, 2 H); 3.70–4.20 (*m*, 1 H); 3.96 (*s*, 3 H).

*(*R*)-3-Benzyloxycarbonylamino-3-diethylphosphonopropionic acid* (**34**). Similarly to the preparation of **35**, 900 mg (2.63 mmol) of **33** were oxidized to **34** to give, after rapid chromatography of the crude product on 50 g silica gel (C), 670 mg (71%) of **34**, Rf(B) 0.29.

*(*R*)-3-Amino-3-phosphonopropionic acid* (**36**). A solution of 300 mg (0.83 mmol) of **34** in 10 ml of a 33% solution of HBr in acetic acid was stirred for 17 h at r.t. After evaporation of the solvents, the crude product was recrystallized from 1 ml of hot water and 5 ml of ethanol yielding 126 mg (90%) of **36**, m.p. 234–237°. $[\alpha]_D^{25} = -32.6$ ($c = 1$, H_2O). – IR. (KBr): 3500–2400 (max), 3490*m*, 3130*s*, 2900*s*, 2830*s*, 1710*s*, 1605*s*, 1505*s*, 1420*m*, 1410*m*, 1332*w*, 1278*s*, 1252*s*, 1200*s*, 1090*s*, 1062*s*, 1030*s*, 970*w*, 925*s*, 895*s*, 880*w*, 869*w*, 752*m*. – ^{1}H-NMR. (90 MHz, D_2O): 2.75–3.45 (*m*, 2 H); 3.70–4.10 (*m*, 1 H). – ^{13}C-NMR. (D_2O): 175.36 (*d*, $J(P,C) = 3.5$); 46.71 (*d*×*d*, $J(P,C) = 145$); 33.94 (*t*).

$C_3H_9NO_5P$	Calc.	C 21.51	H 4.77	N 8.28	P 18.32%
(169.07)	Found	,, 21.58	,, 5.00	,, 8.09	,, 18.09%

*(*R*)-3-Benzyloxycarbonylamino-3-diethylphosphonopropionamide* (**38**). Similarly to the preparation of **35**, 540 mg (1.56 mmol) of **33** were oxidized to **34**. To the residue (480 mg) from the extraction dissolved in 12 ml of THF, at −20°, were added 0.5 ml (4.45 mmol) of *N*-methylmorpholine and 0.4 ml of isobutyl chloroformate (95%, 2.9 mmol). A white precipitate formed, and this mixture was stirred for 11 min at −20° and the treated with 0.7 ml (10 mmol) of 25% aq. NH_3, when the precipitate dissolved. This solution was again stirred for 2.5 h between −20° and +20° and concentrated *i.v.* The residue was diluted with 30 ml of M Na_2CO_3, and the product extracted with CH_2Cl_2 (4×60 ml). The organic phases were washed with M HCl (2×30 ml), 0.5M Na_2CO_3 (30 ml), dried and concentrated *i.v.* Rapid chromatography on 30 mg of silica gel (D) gave 420 mg (75%) of **38**, which was recrystallized in a mixture of hexane and ethyl acetate/ethanol 95:5, m.p. 128–129°. Rf(B) 0.34, $[\alpha]_D^{25} = -15.2$ ($c = 1$, $CHCl_3$). – IR. ($CHCl_3$): 3665*w*, 3530*w*, 3480*m*, 3415*m*, 3340*m*, 3195*m*, 3090*w*, 3060*w*, 3000*s*, 2940*m*, 2910*w*, 2870*w*, 1720*s*, 1680*s*, 1612*m*, 1595*w*, 1503*m*, 1455*m*, 1445*m*, 1395*m*, 1370*w*, 1305*s*, 1260*s*, 1160*m*, 1147*m*, 1100*m*, 1030*s*, 915*s*, 910*w*, 830*w*. – ^{1}H-NMR. (200 MHz, $CDCl_3$): 1.20 (*t*, $J = 7$, 3 H); 1.27 (*t*, $J = 7$, 3 H); 2.61 (*d*, $J = 7$, 1 H); 2.67 (*d*, $J = 7$, 1 H); 3.95–4.20 (*m*, 4 H); 4.50 (*d*×*d*×*d*×*d*, $J = 16$, 10, 7 and 7, 1 H); 5.04 (*d*, $J = 12$, 1 H); 5.12 (*d*, $J = 12$, 1 H); 5.81 (*s*, 1 H); 6.23 (*d*, $J = 10$, exchangeable with D_2O, 1 H, NH); 6.63 (*s*, 1 H); 7.33 (*s*, 5 H). – ^{13}C-NMR. ($CDCl_3$): 172.31 (*d*, $J(P,C) = 16$); 155.95 (*d*, $J(P,C) = 4.5$); 136.33 (*s*); 128.21 (*d*); 127.79 (*d*); 66.82 (*t*); 63.45 (*t*×*d*, $J(P,C) = 7$); 62.54 (*t*×*d*, $J(P,C) = 7.5$); 38.74 (*d*×*d*, $J(P,C) = 165$); 35.32 (*t*×*d*, $J(P,C) = 3$); 16.27 (*qa*×*d*, $J(P,C) = 5.5$).

$C_{15}H_{23}N_2O_6P$	Calc.	C 50.28	H 6.47	N 7.82	P 8.64%
(358.33)	Found	,, 50.37	,, 6.34	,, 7.82	,, 8.47%

(R)-3-Amino-3-phosphonopropionamide (**39**). A solution of 300 mg (0.84 mmol) of **38** in 6 ml of a 33% solution of HBr in acetic acid was stirred for 17 h at r.t. After evaporation of the solvents, the crude product was recrystallized from 4 ml of hot water and 8 ml of ethanol yielding 130 mg (92%) of **39**, m.p. 268–273°. $[\alpha]_D^{25} = -33.0$ ($c = 1$, H_2O). – IR. (KBr): 3500–2000 (max), 3415*s*, 3260*s*, 3160*s*, 2940*s*, 2800*s*, 2660*s*, 2570*s*, 2340*m*, 2090*w*, 1670*s*, 1620*s*, 1500*s*, 1430*s*, 1415*m*, 1320*m*, 1265*m*, 1200*s*, 1165*s*, 1110*m*, 1085*s*, 1065*s*, 1020*s*, 940*s*, 915*s*, 860*w*, 810*m*. – ^{1}H-NMR. (90 MHz, D_2O): 2.87 ($d \times d \times d$, $J = 16$, 9.5 and 8, 1 H, H–C(2)); 3.15 ($d \times d \times d$, $J = 12.5$, 8 and 4, 1 H, H–C(2)); 3.86 ($d \times d \times d$, $J = 14$, 9.5 and 4, 1 H, H–C(3)). – ^{13}C-NMR. (D_2O): 175.25 (*d*, J(P,C) = 14); 46.81 ($d \times d$, J(P,C) = 145); 33.44 (*t*).

REFERENCES

[1] *D. Redmore*, Topics Phosphorous Chem. *8*, 515 (1976).
[2] *K. Prajer & J. Rachon*, Z. Chem. *1975*, 209.
[3] *K.A. Petrov, V.A. Chauzov & T.S. Erokhina*, Russian Chem. Rev. *43*, 984 (1974).
[4] *S. Westerback, K.S. Rajan & A.E. Martell*, J. Am. Chem. Soc. *87*, 2567 (1965).
[5] *H.S. Hendrickson*, Anal. Chem. *39*, 998 (1967).
[6] *J.W. Huber, W.F. Gilmore & L.W. Robertson*, J. Med. Chem. *18*, 106 (1975).
[7] *F.R. Atherton, M.J. Hall, C.H. Hassall, S.W. Holmes, R.W. Lambert, W.J. Lloyd & P.S. Ringrose*, Antimicrob. Agents Chemother. *18*, 897 (1980).
[8] *T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, S. Haga, H. Sugi, K. Tanigawa, Y. Suski, K. Fukawa, O. Irino, O. Saita & S. Yamabe*, Heterocycles *16*, 1205 (1981).
[9] *F.R. Atherton, M.J. Hall, C.H. Hassall, R.W. Lambert, W.J. Jloyd & P.S. Ringrose*, Antimicrob. Agents Chemother. *15*, 696 (1979).
[10] *J.G. Allen, F.R. Atherton, M.J. Hall, C.H. Hassall, S.W. Holmes, R.W. Lambert, L.J. Nisbet & P.S. Ringrose*, Antimicrob. Agents Chemother. *15*, 684 (1979).
[11] *J. Emsley & D. Hall*, in: 'The Chemistry of Phosphorous', Harper & Row, London 1976, p.494.
[12] *J. Zemlicka & S. Chladek*, Collect. Czech. Chem. Commun. *34*, 1007 (1969).
[13] *S. Neale*, Chem. Biol. Interactions *2*, 349 (1970).
[14] *W.J. Gilmore & H.A. McBride*, J. Am. Chem. Soc. *94*, 4361 (1972).
[15] *A. Kotynski & W.J. Stec*, J. Chem. Res. (S) *1978*, 41.
[16] *A. Vasella & R. Voeffray*, J. Chem. Soc., Chem. Commun. *1981*, 97.
[17] *J. Shahak & J. Peretz*, Israel J. Chem. *9*, 35 (1971).
[18] *A. Vasella*, Helv. Chim. Acta *60*, 1273 (1977).
[19] *R.A. Eirestone*, US Patent 3,784,590 (1974).
[20] *J.M.J. Tronchet & E. Mihaly*, Helv. Chim. Acta *55*, 1266 (1972).
[21] *J. Hamer & A. Macaluso*, Chem. Rev. *64*, 473 (1964).
[22] *O. Tsuge, K. Sone & S. Urano*, Chem. Lett. *1980*, 977.
[23] *W. Rundel*, «Methoden der Organischen Chemie», in Houben-Weyl-Müller 10/4, 322, ed. Thieme, Stuttgart 1968.
[24] *A. Vasella, R. Voeffray, J. Pless & R. Huguenin*, in preparation.
[25] *D.M. Vyas, H.C. Jarrell & W.A. Szarek*, Can. J. Chem. *53*, 2748 (1975).
[26] *W.C. Still, M. Kahn & A. Mitra*, J. Org. Chem. *43*, 2923 (1978).
[27] *H. Loibner & G. Seidl*, Chromatographia *12*, 600 (1979).