181. Nucleophilic Additions to *N*-Glycosylnitrones

Asymmetric Synthesis of α-Aminophosphonic Acids[1])

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Dedicated to Professor Dr. *A. Eschenmoser* on the occasion of his 60th birthday

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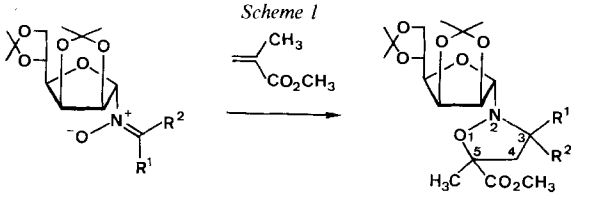
The hypothesis which explains the diastereoselectivity of the 1,3-dipolar cycloaddition of the *N*-glycosylnitrones **1–3** leading to the 5,5-disubstituted isoxazolidines **4–6** on the basis of a kinetic anomeric effect predicts that nucleophiles should add to *N*-glycosylnitrones with a high degree of diastereoselectivity. To test this prediction, the nucleophilic addition of lithium and potassium dialkylphosphites to the crystalline (*Z*)-nitrone **11**, prepared from oxime **9** and (benzyloxy)acetaldehyde has been examined. The addition of *lithium* phosphites gave the *N*-glycosyl-*N*-hydroxyaminophosphonates **12–16** (d.e. 78–92%) in high yields *(Scheme 4)*. The addition of *potassium* phosphites showed a much lower diastereoselectivity. Glycoside cleavage, hydrogenolysis, and dealkylation of **12–16** gave (+)-(*S*)-phosphoserine (+)-**19** (34–45% from **9**). Its absolute configuration was confirmed by an X-ray analysis of the *N*-(3,3,3-trifluoro-2-methoxy-2-phenylpropionyl) derivative **24**. Similarly, the crystalline nitrone **25** gave the *N*-glycosyl-*N*-hydroxyaminophosphonate **26**, which was transformed into (+)-(*S*)-phosphovaline (+)-**31** (42% from **9**). The diastereoselectivity of the nucleophilic addition and the enantiomeric purity of (+)-**31** were determined by the analysis of the derivative **30** (d.e. 92%) and **32** (d.e. 93%), respectively. The addition of lithium diethyl phosphite to the nitrone **33**, prepared *in situ*, gave the *N*-glycosyl-*N*-hydroxyaminophosphonate **34** (41%; d.e. 91%), which was transformed in (+)-(*S*)-phosphoalanine (+)-**37** (21% from **9**).

1. Introduction. – The diastereoselectivity of the 1,3-dipolar cycloaddition of the *N*-glycosylnitrones **1–3** to methyl methacrylate, leading mainly to the (5*S*)-configurated *N*-glycosylisoxazolidines **4–6** *(Scheme 1)* has been rationalized on the basis of stereoelectronic and steric effects [1].

Scheme 1

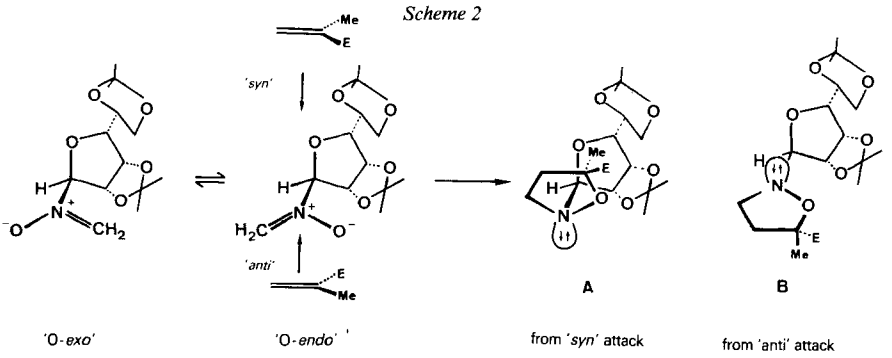


1 $R^1=R^2=H$
2a $R^1=CH_3$ $R^2=H$
2b $R^1=H$ $R^2=CH_3$
3 $R^1=R^2=CH_3$

4 $R^1=R^2=H$
5 $R^1=CH_3$ $R^2=H$
6 $R^1=R^2=CH_3$

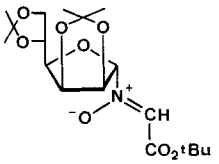
[1]) Parts of this work have been presented at the 5th International Conference on Organic Synthesis in Freiburg i. Br., 27–30/8/1984.

Scheme 2



To a coplanar arrangement of the LUMO of the nitrone π-system and the σ^*-orbital of the C(1)–O bond in the reacting *N*-glycosylnitrones corresponds a coplanar arrangement of the doubly occupied sp^3 orbital on the N-atom and of the σ^*-orbital of the C(1)–O bond in the product. The stabilizing (*exo*)anomeric effect present in the product may already become effective in the transition state and lower its energy. These orbital interactions are possible starting with either the 'O-*endo*' or the 'O-*exo*' conformers of the nitrones (*Scheme 2*), but the sterically less congested 'O-*endo*' conformer seems to react preferentially [1]. The (5*S*)-configuration of the principally formed *N*-glycosylisoxazolidines may result either from an attack of the dipolarophile from the side of the C–O bond ('*syn*' in *Scheme 2*) with an *endo*-orientation of the methacrylate methyl group or of an attack of the dipolarophile from the side opposite to the C–O bond ('*anti*' in *Scheme 2*) with an *exo*-orientation of the methacrylate CH_3 group. Although it was not possible to decide between these two possibilities, the former one leading to an antiperiplanar arrangement of lone-pair and polar bond (**A** in *Scheme 2*) seemed to be stereoelectronically preferred.

The lower diastereoselectivity related to the formation of the center at C(3) in **5** (d.e. 38.5%) and the modest diastereoselectivity (d.e. < 55%) of the cycloaddition to ethylene of the nitrones **7** and **8**, leading to α-aminocarboxylic and α-aminophosphonic acids, respectively, may be rationalized by an (*E*)/(*Z*)-equilibration of the nitrones, occuring easily under thermal conditions [1–3]. To obtain high diastereoselectivities, the use of diastereoisomerically pure nitrones under reaction conditions which exclude (*E*)/(*Z*)-equilibration seems mandatory.



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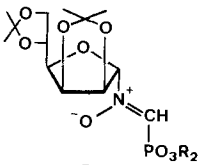

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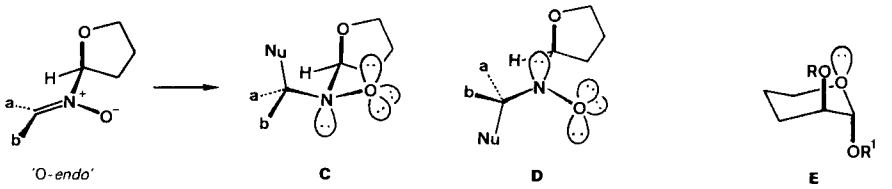
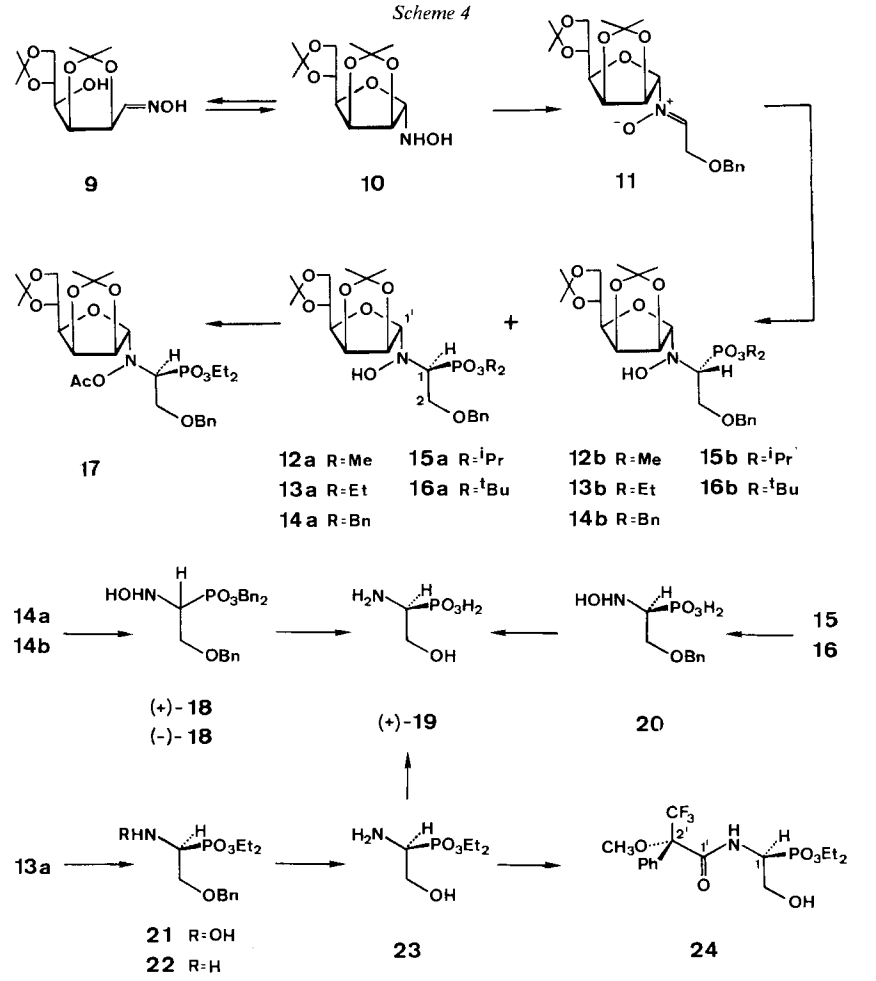
2. Plan and Results. – The addition of a nucleophile to an *N*-glycosylnitrone yields *N*,*N*-disubstituted hydroxylamines [4] [5]. In the course of the addition, a doubly occupied, nonbonding sp^3 orbital at the N-atom is formed, which may be coplanar with the C(1)–O bond and interact with its σ^*orbital (*Scheme 3*). Obviously, there is an analogy between a LUMO-controlled 1,3-dipolar cycloaddition of a *N*-glycosylnitrone and the addition of a nucleophile to it. The kinetic anomeric effect should again lead to a selective lowering of those transition states in which a lone pair-polar bond interaction is possible (**C** and/or **D** in *Scheme 3*). The kinetic anomeric effect should be particularly strong due

Scheme 3



to a conjugative interaction of the lone pairs at N and O of the developing hydroxylamino anion. This situation is 'inversely analogous' to the one found in glycosides of the α-D-mannopyranosyl type (partial structure **E** in *Scheme 3*). These glycosides show a stronger anomeric effect then α-D-glucopyranosides, an observation which may be explained by a conjugative interaction of the σ*orbitals of the C(1)–O and the C(2)–O bonds [6]. The picture is certainly complicated by the interaction of the developing

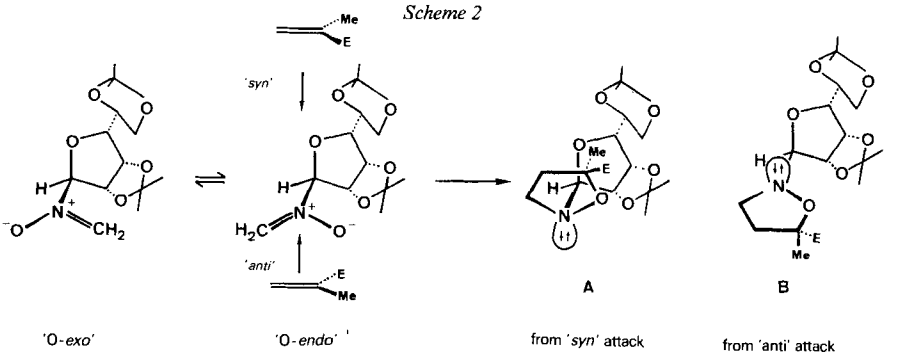
Scheme 4



hydroxylamino anion with the counterion, but the addition of nucleophiles to *N*-glycosylnitrones is expected to be a highly diastereoselective reaction.

Phosphite anions as nucleophiles should lead to esters of *N*-hydroxy-*N*-glycosyl-α-aminophosphonic acids, which might be transformed further into enantiomerically pure *N*-hydroxy-α-aminophosphonic and into α-aminophosphonic acids[2][3]). The *N*-hydroxy-α-aminophosphonic acids and α-aminophosphonic acids, analogs of the corresponding amino acids, exert biological activities, which have been shown to depend on the absolute configuration [8] [9] of the acids. Enantiomerically pure α-aminophosphonic acids have been obtained either by the resolution of enantiomers [10–13] or by asymmetric synthesis

Scheme 2



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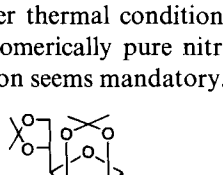

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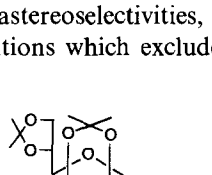

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Table 1. *Selected Data of the Diastereoisomers* **a** *and* **b** *of the* N-*Glycosyl-α-amino-phosphonates* **12–16**

	^{13}C-NMR δ[ppm], J(C,P)[Hz] of C(1)	^{31}P-NMR: δ[ppm]	$[\alpha]_D^{25}$
12a	60.0 (151.4)	26.9	+24.5°
12b	59.1 (165.7)	27.2	+14.6°
13a	60.4 (151.6)	24.1	+27.7°
13b	59.5 (166.5)	24.5	+13.4°
14a	60.7 (151.6)	25.2	+16.2°
14b	59.8 (165.5)	25.6	+18.4°
15a	60.8 (154.4)	22.0	+26.7°
15b	59.9 (167.1)	23.0	+16.6°
16a	62.4 (155.1)	14.8	+26.5°
16b	–	16.7	–

HPLC (*Zorbax*-Sil). During chromatography, the diisopropyl phosphonate **15b** decomposed partially and the di(*tert*-butyl) phosphonate **16b** completely. The diastereoisomers **a** and **b** of **12–16** differ in the chemical shift of the C(1) signals (^{13}C-NMR) and of the P signals (^{31}P-NMR), while the low value of J(1′,2′) (0–1 Hz) in the ^{1}H-NMR spectra of all products are characteristic for their α-D-configuration (see *Table 1*).

The diastereoisomeric excess in the crude mixtures of the *N*-glycosyl-α-amino-phosphonates **12–16** was first determined by ^{31}P-NMR spectroscopy. The relaxation times of the ^{31}P nuclei in pairs of diastereoisomers appeared to be quite similar[4]). High induction rendered the integration of the minor peak difficult, by-products and side bands of the major peak interferring. The determination of the d.e. by HPLC of the dimethyl, diethyl and dibenzyl *N*-glycosyl-α-aminophosphonates **12–14**, obtained by the addition of the corresponding lithium phosphite to nitrone **11**, gave reproducible values in accordance with the results from the ^{31}P-NMR spectra. The addition of potassium phosphite to **11** gave more complex mixtures, and HPLC failed to give reliable results (by-products and decomposition).

The crude mixtures of the diisopropyl and di(*tert*-butyl) *N*-glycosyl-α-amino-phosphonates **15** and **16**, respectively, were also transformed into (+)-phosphoserine (+)-**19**. In the first step of the degradation, the chiral auxiliary was removed quantitatively and the enrichement of one enantiomer was not expected[5]). The diastereoselectivity of the phosphite addition was thus deduced from the optical rotation[5]).

In CH_2Cl_2 solution at −60°, lithium diethyl, diisopropyl, and di(*tert*-butyl) phosphite added with about equal selectivity (d.e. 85 ± 2% by HPLC or opt. purity, 87 ± 4% by ^{31}P-NMR, *Table 2*), whilst the selectivity of the addition of lithium dimethyl phosphite is slightly lower, indicating little, if any, dependence on the size of the phosphite alkyl

[4]) Integration of the peaks in the ^{31}P-NMR spectra of a sample of **12** *(Scheme 4)*, prepared by mixing equal amounts of **12a** and **12b** gave a d.e. of 5%. Similarly, a d.e. of 6% (HPLC ±1%) was found for a sample of **30** *(Scheme 5)*, prepared from racemic diethyl phosphovaline, but one of 0% for a sample of **32**, prepared from racemic phosphovaline **31** [26].

[5]) ^{31}P-NMR and HPLC analysis of the dibenzyl α-aminophosphonate **14** and the specific rotation of a sample of (+)-phosphoserine (+)-**19** obtained from **14** gave equivalent results. The $[\alpha]_D^{25}$ value for (+)-**19**, prepared from **14**, assumed to be enantiomerically pure, was +30° (c = 1, H_2O). This value was taken as a reference.

Table 2. *The Diastereoisomeric Excess of the* N-*Hydroxy*-N-*glycosyl*-α-*aminophosphonates* **12–16**, *Obtained by the Addition of Lithium and Potassium Phosphites to* **11** *at* −60°

Anion $LiPO_3R_2$	Solvent	Diastereoselectivity (d.e.) determined by			Anion KPO_3R_2	Solvent	Diastereo-selectivity (d.e.)
		^{31}P-NMR	HPLC	$[\alpha]_D^{25}$ of **19**			^{31}P-NMR
R=CH_3	CH_2Cl_2	77%	78%	–	R=CH_3	CH_2Cl_2	58–67%
	THF	91%	90%	–		THF	70%
R=CH_3CH_2	CH_2Cl_2	89–91%	87%	–	R=CH_3CH_2	CH_2Cl_2	64–77%
	THF	91%	92%	–		THF	78%
R=Bn	CH_2Cl_2	79–83%	80–83%	80%	R=Bn	CH_2Cl_2	52%
	THF	83%	86%			THF	–
R=$(CH_3)_2CH$	CH_2Cl_2	83–88%	–	84%	R=$(CH_3)_2CH$	CH_2Cl_2	11–50%
R=$(CH_3)_3C$	CH_2Cl_2	91%	–	86%	R=$(CH_3)_3C$	CH_2Cl_2	22–28%

moiety. In THF solution, the difference in diastereoselectivity between lithium dimethyl and diethyl phosphite disappeared and the d.e. increased to 91% (HPLC).

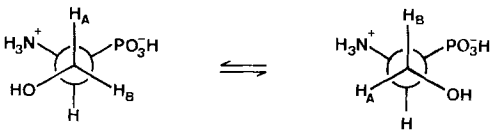
The addition of potassium phosphites to **11** gave erratic results *(Table 2)*; the d.e. being always lower than the one observed for the lithium salts, especially with the bulkier phosphites[6]).

Phosphoserine (+)-**19** was best prepared from the dibenzyl or di(*tert*-butyl) α-aminophosphonates **14a** and **16a.** The addition of lithium dibenzyl phosphite to **11** gave a mixture **14a**/**14b** (92%), from which the major diastereoisomer **14a** was obtained pure after three crystallisations (63%, d.e. 98.7%).

The ^{31}P-NMR spectrum of **14a** is characterized by a *s* at 25.2 ppm. In the ^{13}C-NMR spectrum, the signal of C(1) appears at 60.7 ppm (J(C,P) = 151.4 Hz) and that of C(2) at 67.2 ppm (J(C,P) = 5.8 Hz). In the glycosyl moiety, a P,C coupling is only found for C(1') (97.2 ppm, J = 11 Hz). In the ^{1}H-NMR spectrum, the signal of H–C(1) appears at 3.75 ppm (J(H,P) = 18.1 Hz).

Hydrolysis of **14a** with 1N HCl/MeOH gave the crystalline, protected (+)-*N*-hydroxyphosphoserine (+)-**18** (85%). Similarly, the minor diastereoisomer **14b** was transformed into (−)-**18**. Hydrogenation (10% Pd/C) of (+)-**18** gave crystalline (+)-**19** ($[\alpha]_D^{25}$ = +30° (*c* = 1, H_2O), overall yield from **9** 34%)[7]).

In the ^{1}H-NMR spectrum of (+)-**19**, the value of 14.2 Hz for J(H,P) allows to attribute the signal at 3.38 ppm to H–C(1). Phosphoserine appears to exist preferentially in the conformation **F**. This is evidenced by J(H,P) = 4.1



F **G**

[6]) Reaction under an O_2-free N_2 atmosphere gave a lower induction than under dry air (for **13**: 64% instead of 77%; for **15**: 11–30% instead of 50%). This may indicate a competitive radical (SET) mechanism, perhaps correlated with a lower complexing ability of K^+ and also with a lower nucleophilic reactivity of the phosphite salt. Potassium di(*tert*-butyl) phosphite did not react below −40°.

[7]) *Mastalerz* and coworkers [27] reported the synthesis of (+)-phosphoserine (+)-**19** *via* resolution of racemic diethyl 1-bromo-2-aminoethanephosphonate. The (*S*)-configuration of (+)-**19** $[\alpha]_{578}^{20}$ = +27° (*c* = 2.5, H_2O)) was determined by chemical correlation.

and 5.5 Hz for H_A (4.02 ppm) and H_B (3.78 ppm), respectively, requiring an H,C,C,P torsion angle < 90° [28] [29] and also by $J(H_A,H_C) = 10$ and $J(H_B,H_C) = 4$ Hz. $J(H_A,P)$ expected for conformer **G** [29] is 20–35 Hz.

The addition of lithium di(*tert*-butyl) phosphite [30] to **11** at −60° gave the major diastereoisomer **16a** in 68% yield after crystallisation.

The ^{31}P-NMR spectrum of **16a** shows a chemical shift of 14.9 ppm. The difference to **14a** (25.2 ppm) is partially due to a σ-donor effect of the *t*-Bu groups, but also to steric interactions influencing the P–O bond angles and the π character of the P=O bond [31]. (For comparison with the dimethyl, diethyl, and diisopropyl α-aminophosphonate see *Table 1.*)

Hydrolysis of **16a** gave the *O*-benzyl-1-decarboxy-*N*-hydroxy-1-phosphoserine (**20**), which was hydrogenated (Pd) to give (+)-phosphoserine (+)-**19** (45% from **9**). After chromatography on *Dowex 50* (H^+) and lyophilisation, chromatographically pure (+)-**19** was obtained as a foam ($[\alpha]_D^{25} = +28°$ ($c = 1.4$, H_2O)), crystallizing in contact with MeOH (m.p. 210–212°, $[\alpha]_D^{25} = +30$ ($c = 1.7$, H_2O)). The (*S*)-configuration of the (+)-**19** was confirmed by an X-ray analysis of the substituted trifluoropropionamide **24**[8]) *(Fig. 2)*.

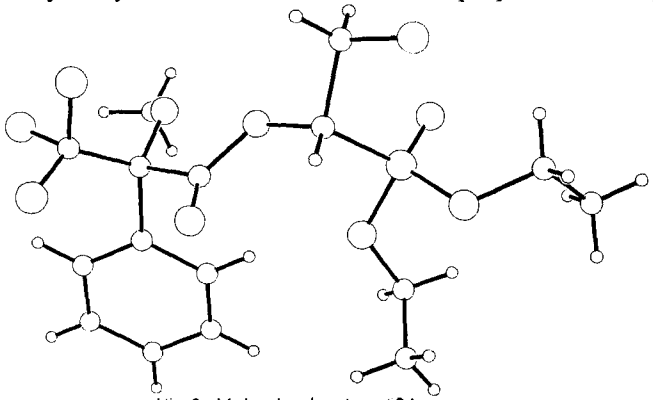


Fig. 2. *Molecular drawing of* **24**

Crystallographic data have been deposited at the *Cambridge Crystallographic Data Center*. Monoclinic space group $P2_1$: $a = 11.571(7)$, $b = 8.468(7)$, $c = 19.812(11)$ Å, $\beta = 98.83(5)°$; $Z = 4$, D(calc.) = 1.43 g/cm^3. Intensity measurements at 170° K were made with a *Nicolet-R-3m* four-circle diffractometer (graphite monochromator, MoK_α, $\lambda = 0.71069$ Å). The structure has been solved by the heavy-atom method; SHELXTL [24]. The crystals were of poor quality and showed signs of decomposition during the measurement. Split spots on an oscillation photograph after the data collection confirmed the observation. The final refinement was carried out with isotropic thermal parameters, because attempts to refine anisotropically gave physically unreasonable values for the EtO-groups. The final *R* value was 0.17. In spite of this, there seems to be no reason to doubt the general structural features and in particular the relative configuration of atoms C(1) and C(2').

The hydrolysis of the diethyl phosphoserine **23** with conc. HCl to (+)-**19** (32% from **9**) proceeded with a slight loss of optical purity ($[\alpha]_D^{25} = +26.4°$ ($c = 1.1$, H_2O)). The dealkylation of **23** with trimethylsilyl bromide [33] gave (+)-**19** with an $[\alpha]_D^{25} = +28.0°$ ($c = 2.5$, H_2O) after lyophilisation.

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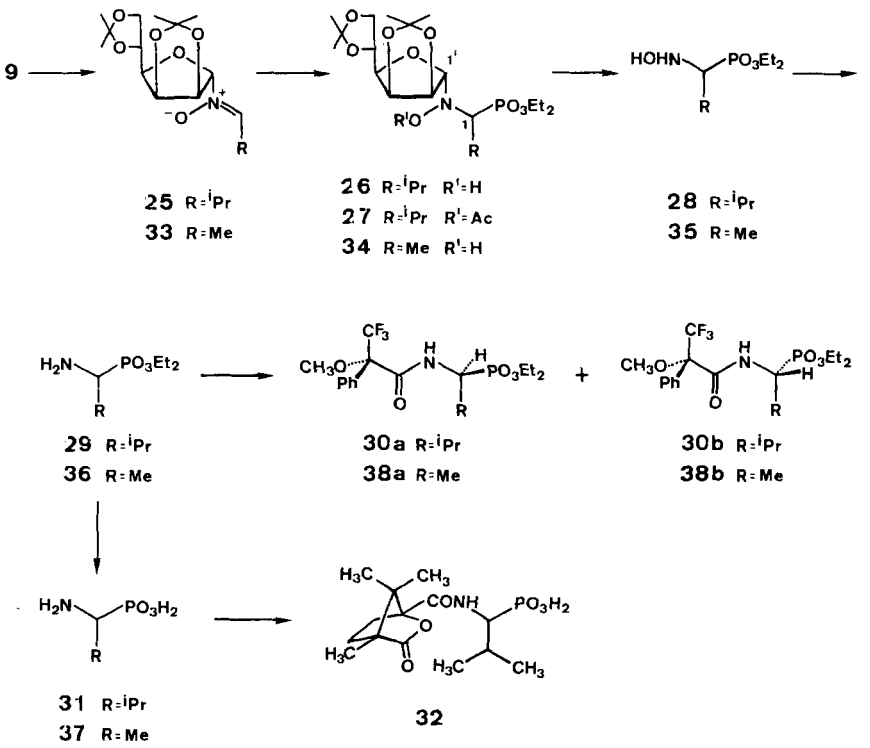
[8]) Amide **24** was obtained as follows *(Scheme 4)*: Addition of lithium diethyl phosphite to **11** (CH_2Cl_2, −60°) yielded **13a** (66%, after crystallisation; characterized as the O-acetyl derivative **17**), which was hydrolysed to the stable, protected (+)-1-decarboxy-*N*-hydroxy-1-phosphoserine (**21**; 95%). Hydrogenation of **21** (Pd/C) gave **23** (67%), which reacted with (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionylchloride [32] to give **24** (74%). Incomplete hydrogenation of **21** gave **22** as a by-product.

Phosphovaline. The nitrone **25** *(Scheme 5)*, suitable for the synthesis of phosphovaline **31**, was obtained from the condensation of isobutyraldehyde and the oxime **9** as a crystalline, diastereoisomerically pure and slowly decomposing compound (85%). A strong nuclear *Overhauser* effect between H–C(1) and H–C(1') confirms its (*Z*)-configuration. The addition of lithium diethyl phosphite to **25** in CH_2Cl_2 solution at −70° gave the *N*-glycosyl-α-aminophosphonate **26**[9]) in 61% yield after crystallisation. No reaction was observed with potassium diethyl phosphite.

Scheme 5



In the ^{1}H-NMR spectrum of **26**, the signal of H–C(1) (3.22 ppm) is characterized by J(H,P) of 17.5 Hz. In the ^{13}C-NMR spectrum, the signals of C(1), C(2), and C(1') are found at 64.8 (J(C,P) = 137.1), 28.6 (J(C,P) = 5.0), and 98.0 ppm (J(C,P) = 2.9 Hz), respectively. Only one signal at 27.5 ppm was found in the ^{31}P-NMR spectra of crude **26**, even if the phosphite addition was carried out at 0°, indicating that both (expected) diastereoisomers could have an identical chemical shift.

The d.e. of **26**, which shows no useful UV absorbtion above 200 nm, was determined with the help of a derivative. From racemic diethyl phosphovalinate (±)-**29** [34] and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride, we obtained a 1:1 diastereoisomeric mixture of the amides **30a**/**30b** (87%), distinguishable by ^{31}P-, ^{13}C- and ^{1}H-NMR and also by HPLC *(Zorbax-Sil)*.

[9]) Characterized as the *O*-acetyl derivative **27**.

In the ^{1}H-NMR spectra of **30a**/**30b**, the CH_3O signals appear at 3.38 ppm (J(C,F) = 1.3 Hz) and at 3.52 ppm (J(C,F) = 1.5 Hz). The N*H* signal shows 2*d* (J = 12 Hz) at 7.18 and 6.85 ppm, and the ^{31}P-NMR is characterized by two signals at 24.09 and 24.02 ppm.

Hydrolysis of the *N*-glycosyl-α-aminophosphonate **26**, followed by hydrogenation (10% Pd/C) gave the optically active diethyl phosphovalinate (+)-**29** (94% from **26**) *via* the unstable *N*-hydroxy-α-aminophosphonate **28**. The d.e. of **30a**/**30b** obtained from the crude *N*-glycosyl-α-aminophosphonate **26** was 93% (HPLC and ^{31}P-NMR), and we accepted this value for the diastereoselectivity of the phosphite addition reaction. The d.e. of **30** obtained from recrystallized **26** was 99.3% (HPLC).

Acid hydrolysis of the diethyl ester (+)-**29**, obtained from recrystallized **26**, gave (+)-phosphovaline **31** establishing its (*S*)-configuration[10]) [18]. The enantiomeric purity of this sample was checked by preparing the camphanic amide **32** from (+)-**31** and (−)-camphanoyl chloride [36]. The amide **32** showed a d.e. of 92% (by ^{31}P-NMR). From racemic phosphovaline (±)-**31** [26], we obtained a 1:1 mixture of **32**. Apparently, the acid hydrolysis of (+)-**29** had proceeded with a slight loss of enantiomeric purity.

Phosphoalanine. The formation of the nitrone **33** from the oxime **9** and acetaldehyde was indicated by a *q* (7.0 ppm, J = 7 Hz) for H–C(1) in the ^{1}H-NMR spectrum of the crude product, but **33** could not be isolated. The crude product was freed from excess acetaldehyde and treated with lithium diethyl phosphite at −70° to yield the *N*-glycosyl-α-aminophosphonate **34** (41%) as an oil. Hydrolysis of crude **34**, followed by hydrogenation gave, *via* **35**, the diethyl phosphoalanine (+)-**36**, which was transformed into (+)-(*S*)-phosphoalanine (+)-**37**[11]) (72% from (+)-**36**, $[\alpha]_D^{20} = +15.8°$ (c = 1, 1N NaOH)). The diastereoselectivity of the addition was deduced from the optical purity of (+)-**37** (90–95%) and from the d.e. of the amide mixture **38** (91.5% by HPLC), prepared from (+)-**36** as described above. A 1:1 mixture of the diastereoisomers **38a**/**38b** was obtained from racemic diethyl phosphoalanine (±)-**36** [35]. The two diastereoisomers **38a**/**38b** have similar spectroscopic data like the phosphovaline analogs **30a**/**30b**, but cannot be distinguished in the ^{31}P-NMR spectrum (25.3 ppm).

Since the yield in which the (*E*)- and/or (*Z*)-configurated nitrones **33** were formed is not known, it is difficult to comment upon the yield and diastereoselectivity of the addition reaction. But the experiment shows that a good induction may be obtained, even if the necessary nitrone cannot be isolated and crystallized.

A comparison of the stereochemistry of the nucleophilic addition of phosphite anions to N-glycosylnitrones with the one of LUMO-controlled cycloadditions of such nitrones will be reported in a separate publication.

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[10]) This sample showed an $[\alpha]_D^{25} = -0.8°$ (c = 1.99, 1N NaOH), (+)-(*S*)-phosphovaline corresponding to (−)-(*S*)-disodium phosphovalinate. Originally, an $[\alpha]_D$ value of −10° was reported for this salt [18]. In 1983, *Kafarski et al.* [13] reported a corrected value for (−)-disodium phosphovalinate ($[\alpha]_{578}^{20} = -0.6 \pm 0.2°$ (c = 1, 1N NaOH)).

[11]) *Atherton et al.* [11] determined the absolute configuration of (+)-(*S*)-phosphoalanine ($[\alpha]_D^{20} = +16.8°$ (c = 2, 1N NaOH)) obtained by resolution of the enantiomers.

Experimental Part

General. See [20]. $CHCl_3$ was filtered through neutr. Al_2O_3, CH_2Cl_2 was distilled from P_2O_5. *t*-BuOLi and *t*-BuOK were freshly sublimed. N_2 was dried (self-indicating silica gel) and deoxygenated (BTS catalyst, *Fluka*). Usual workup implies drying of the org. phases ($MgSO_4$) and concentration in a rotary evaporator under reduced pressure below 40°. Compounds on TLC plates were detected by spraying the plates with a 0.02M soln. of I_2 in 10% aq. H_2SO_4 or (for amines) by spraying with ninhydrin soln. (290 ml of *s*-BuOH, 100 ml of H_2O, 10 ml of AcOH, 1.6 g of ninhydrin), or by dipping them into 10% phosphomolybdic acid in EtOH, followed by heating at *ca.* 200°. For chromatography, the following solvent mixtures were used: A = CH_2Cl_2/MeOH 19:1, B = BuOH/EtOH/NH_3/H_2O 3:3:3:1. Anal. HPLC (column size 250 × 4.6 mm) was performed on a *Kontron* (LC pump *410*) and prep. HPLC (column size 250 × 21.2 mm) on a *Du Pont 8800* apparatus, with UV detection at 254 nm. The integrals of the peaks of diastereoisomeric pairs determined by HPLC or by ^{31}P-NMR are written in brackets behind the retention times or the chemical shifts, respectively. IR: *Perkin-Elmer-298* spectrometer ($CHCl_3$ soln. 3–5%, unless otherwise specified). ^{1}H-NMR, ^{13}C-NMR, and ^{31}P-NMR: *Varian HA 100* (^{13}C(25 MHz)), *Varian XL-200* (^{1}H(200 MHz), ^{13}C(50MHz), ^{31}P(81 MHz)), or *Bruker AM-400* (^{1}H-NMR(400 MHz), ^{13}C(101 MHz), ^{31}P(162 MHz)), in $CDCl_3$ (unless otherwise specified); δ's in ppm relative to TMS (for ^{1}H-NMR and ^{13}C-NMR) as internal standard or relative to H_3PO_4 (for ^{31}P-NMR) as external reference (uncorrected).

1. *2-Benzyloxy-*N*-(2,3:5,6-di-*O*-isopropylidene-α-*D*-mannofuranosyl)ethanimine* N*-Oxide* (**11**). A soln. of **9** (251.3 mg, 1.0 mmol) in $CHCl_3$ was treated with benzyloxyacetaldehyde (150 µl, 1.06 mmol). After 15 h, $MgSO_4$ was added. Usual workup and recrystallisation from EtOAc/hexane gave 353 mg (86.5%) of **11**. M.p. 137°, R_f (EtOAc/hexane 1:1) 0.17. $[\alpha]_D^{20} = +31.7°$ (*c* = 1, $CHCl_3$). UV ($CHCl_3$): 236 (3500). IR (KBr): 3070*m*, 3020*m*, 2980*m*, 2950*m*, 2920*m*, 2895*m*, 2860*m*, 1611*m*, 1598*w*, 1489*w*, 1450*m*, 1438*m*, 1387*s*, 1364*s*, 1357*s*, 1330*w*, 1315*m*, 1289*w*, 1281*s*, 1260*s*, 1245*s*, 1205*s*, 1159*s*, 1120*s*, 1089*s*, 1072*s*, 1058*s*, 1049*s*, 1015*m*, 982*m*, 949*w*, 920*m*, 900*m*, 862*s*, 849*s*, 819*m*, 796*m*, 780*w*, 737*s*, 695*s*, 639*w*, 619*w*. ^{1}H-NMR: 7.3 (br. *s*, Ph); 7.27 (*t*, *J* = 4.4, H–C(1)); 5.27 (*s*, H–C(1')); 5.20 (*d*, *J* = 5.9, H–C(2')); 4.89 (*dd*, *J* = 6.0, 3.7, H–C(3)); 4.58 (*s*, PhCH_2); 4.5–4.3 (*m*, 4 H); 4.1–4.0 (*m*, H–C(6)); 1.50 (*s*, CH_3); 1.45 (*s*, CH_3); 1.38 (*s*, CH_3); 1.35 (*s*, CH_3). ^{13}C-NMR: 136.7 (*d*); 135.8 (*d*); 128.0 (*d*); 127.5 (*d*); 127.4 (*d*); 112.6 (*s*); 108.3 (*s*); 101.3 (*d*); 84.8 (*d*); 83.8 (*d*); 79.6 (*d*); 73.3 (*t*); 72.7 (*d*); 66.0 (*t*); 64.9 (*t*); 26.4 (*q*); 25.6 (*q*); 24.8 (*q*); 24.1 (*q*). Anal. calc. for $C_{21}H_{29}NO_7$ (407.47): C 61.90, H 7.17, N 3.44; found: C 61.81, H 7.20, N 3.38.

2. *General Procedures for the Preparation of* N*-Hydroxy-α-aminophosphonates* **12–16**. 2.1. Under N_2, the phosphite (1 mmol) was added to a soln. of **11** (200 mg, 0.5 mmol) in CH_2Cl_2 (4 ml). *t*-BuOLi (36 mg, 0.45 mmol) or *t*-BuOK (52 mg, 0.45 mmol) was introduced at −60°. The mixture was allowed to warm to −20° (2 h), quenched with H_2O (2 ml) at that temp. diluted with CH_2Cl_2 (75 ml), and washed with H_2O (2 × 15 ml). Usual workup gave a crude product, which was stored at −20°.

2.2. Same procedure as *2.1*, but with THF as solvent.

2.3. *t*-BuOLi (36 mg, 0.45 mmol) or *t*-BuOK (52 mg, 0.45 mmol) was added to a soln. of the phosphite (1 mmol) in CH_2Cl_2 (4 ml) under N_2 at −20°. The mixture was cooled to −60°, treated with a soln. of **11** (200 mg, 0.5 mmol) in CH_2Cl_2 (0.4 ml) and allowed to warm to −20° (2h). Workup as in *2.1*.

3. *Dimethyl {(1*S*)- and (1*R*)-2-Benzyloxy-1-[*N*-(2,3:5,6-di-*O*-isopropylidene-α-*D*-mannofuranosyl)-*N*-hydroxyamino]ethyl}phosphonate* (**12a** and **12b**, resp.). 3.1. To a soln. of **11** (820 mg, 2 mmol) in CH_2Cl_2 (20 ml), dimethyl phosphite (0.8 ml, 8 mmol) was added and then *t*-BuOK (58 mg, 0.5 mmol) at −20°. After 10 min, the mixture was washed with H_2O. Usual workup gave a crude product, which was crystallized from CH_2Cl_2/hexane to yield 600 mg (60%) of **12a** (diastereoisomerically pure by ^{31}P-NMR). Isomer **12b** was obtained by HPLC of the mother liquor (conditions see **12a**, 14 ml/min).

12a: M.p. 133°, R_f (A) 0.31. HPLC (*Zorbax-Sil*, hexane/CH_2Cl_2/MeOH 80:20:1.8, 2 ml/min): t_R 13.25 min. $[\alpha]_D^{25} = +24.5°$ (*c* = 1.0, $CHCl_3$). IR: 3660*w*, 3550*w*, 3300*w* (br.), 3090*w*, 3060*w*, 3030*w*, 2995*s*, 2955*m*, 2880*w*, 2850*w*, 2450*w*, 1490*w*, 1454*m*, 1382*s*, 1372*s*, 1160*w*, 1115*s*, 1065*s*, 1035*s*, 978*m*, 949*w*, 890*w*, 860*m*. ^{1}H-NMR: 7.4–7.2 (*m*, Ph); 6.57 (*s*, OH, exch. D_2O); 4.98 (*d*, *J* = 6.2, H–C(2')); 4.93 (*s*, H–C(1')); 4.80 (*dd*, *J* = 6.2, 3.8, H–C(3')); 4.55 (*s*, PhCH_2); 4.4–4.25 (*m*, H–C(5')); 4.20 (*dd*, *J* = 7.2, 3.8, H–C(4')); 4.15–3.80 (*m*, H–C(6'), H–C(1)); 3.74 (*d*, *J*(H,P) = 10.5, CH_3O); 3.70 (*d*, *J*(H,P) = 10.5, CH_3O); 1.46 (*s*, CH_3); 1.38 (*s*, CH_3); 1.35 (*s*, CH_3); 1.31 (*s*, CH_3). ^{13}C-NMR: 137.7 (*s*), 128.2 (*s*); 127.5 (*s*); 112.2 (*s*); 108.9 (*s*); 99.1 (*dd*, *J*(C,P) = 10.6), 84.3 (*d*); 83.5 (*d*); 80.4 (*d*); 73.5 (*d*); 73.2 (*t*); 67.1 (*dt*, *J*(C,P) = 5.7); 66.7 (*t*); 60.0 (*dd*, *J*(C,P) = 151.4); 53.0 (*dq*, *J*(C,P) = 6.9); 52.8 (*dq*, *J*(C,P) = 6.5); 26.8 (*q*); 26.0 (*q*); 25.3 (*q*); 24.5 (*q*). ^{31}P-NMR: 26.9. Anal. calc. for $C_{23}H_{36}NO_{10}P$ (517.51): C 53.38, H 7.01, N 2.71; found: C 53.41, H 7.29, N 2.67.

12b: R_f as **12a**, HPLC (conditions see **12a**): t_R 12.5 min. $[\alpha]_D^{25} = +14.6°$ (*c* = 0.9, $CHCl_3$). IR: 3555*w*, 3480*w* (very br.), 3090*w*, 3060*w*, 3030*w*, 2990*m*, 2938*m*, 2880*w*, 2850*w*, 2450*w* (br.), 1600*w*, 1490*w*, 1475*w*, 1451*m*, 1381*m*,

1371*m*, 1156*m*, 1145*m*, 1110*s*, 1000*s*, 1045*s*, 975*m*, 950*m*. ^{1}H-NMR: 7.35–7.25 (*m*, Ph); 6.23 (*s*, OH, exch. D_2O); 5.03 (*d*, *J* = 6.1, H–C(2′)); 4.93 (*s*, H–C(1′)); 4.82 (*dd*, *J* = 3.7, 6.0, H–C(3′)); 4.54 (*s*, $PhCH_2$); 4.34 (*m*, H–C(5′)); 4.17 (*dd*, *J* = 3.6, 7.2, H–C(4′)); 4.1–3.8 (*m*, H–C(6′), H–C(2), H–C(1)); 3.78 (*d*, *J*(H,P) = 10.7, CH_3O); 3.75 (*d*, *J*(H,P) = 10.7, CH_3O); 1.48 (*s*, CH_3); 1.42 (*s*, CH_3); 1.37 (*s*, CH_3); 1.34 (*s*, CH_3). ^{13}C-NMR: 137.6 (*s*); 128.5–127.7 (*m*); 112.3 (*s*); 109.1 (*s*); 97.3 (*dd*, *J*(C,P) = 14.5); 84.3 (*d*); 83.4 (*d*); 80.5 (*d*); 73.5 (*d*); 73.2 (*t*); 66.9 (*t*); 65.4 (*dt*, *J*(C,P) = 6.0); 59.1 (*dd*, *J*(C,P) = 165.7); 53.2 (*dq*, *J*(C,P) = 6.9); 53.0 (*dq*, *J*(C,P) = 6.9); 26.9 (*s*); 26.1 (*s*); 25.3 (*s*); 24.6 (*s*). ^{31}P-NMR: 27.16.

3.2. *With* t-*BuOLi and* CH_2Cl_2. See *2.1*. Data of the crude mixture: HPLC (conditions see **12a**): **12a**: 14.88 min (8.22); **12b**: 14.08 min (1.00). ^{31}P-NMR: **12a**: 26.94 (7.90); **12b**: 27.10 (1.00).

3.3. *With* t-*BuOK and* CH_2Cl_2. See *2.1*. Data of the crude mixture: HPLC (conditions see **12a**): **12a**: 14.82 min (4.18); **12b**, 14.03 min (1.00). ^{31}P-NMR: **12a**: 26.85 (4.95); **12b**: 27.11 (1.00).

3.4. *With* t-*BuOLi and THF*. See *2.2*. Data of the crude mixture: HPLC (conditions see **12a**): **12a**: 13.58 min (21.1); **12b**: 12.97 min (1.00). ^{31}P-NMR: **12a**: 26.82 (19.5); **12b**: 27.13 (1.00).

3.5. *With* t-*BuOK and THF*. See *2.2*. Data of the crude mixture: HPLC (conditions see **12a**): **12a**: 14.01 min (5.28); **12b**: 13.12 min (1.00). ^{31}P-NMR: **12a**: 26.87 (5.7); **12b**: 27.12 (1.00).

4. *Diethyl {(1S)- and (1R)-2-Benzyloxy-1-[*N*-(2,3:5,6-di-*O*-isopropylidene-α-*D*-mannofuranosyl)-*N*-hydroxyamino]ethyl}phosphonate* (**13a** and **13b**, resp.). 4.1. *With* t-*BuOLi and* CH_2Cl_2. See *2.1*. Diethyl phosphite (40 ml, 0.3 mol), **11** (40.7 g, 0.1 mol), CH_2Cl_2 (1 l), and *t*-BuOLi (5 g, 0.07 mol). The crude product was crystallized in CH_2Cl_2/hexane to afford 36 g (66%) of **13a** (diastereoisomerically pure by ^{31}P-NMR). Isomer **13b** was obtained by HPLC of the mother liquor (*Zorbax-Sil*, hexane/CH_2Cl_2/MeOH 40:10:1, 16 ml/min, t_R 9.8 min).

13a: M.p. 152°, R_f (A) 0.4. HPLC (*Zorbax-Sil*, hexane/CH_2Cl_2/MeOH 100:5:2, 2 ml/min): t_R 15 min. $[\alpha]_D^{25}$ = +27.7° (*c* = 1, $CHCl_3$). IR: 3660*w*, 3560*w*, 3400*w* (br.), 3080*w*, 2990*s*, 2930*s*, 2910*m*, 2900*m*, 2880*w*, 2450*w* (br.), 1680*w*, 1600*w*, 1550*w*, 1500*m*, 1380*s*, 1370*s*, 1160*s*, 1065*s*, 1025*s*, 970*s*, 905*s*, 885*w*. ^{1}H-NMR: 7.4–7.2 (*m*, Ph); 6.41 (*s*, NOH, exch. D_2O); 4.98 (*d*, *J* = 6, H–C(2′)); 4.96 (*s*, H–C(1′)); 4.80 (*dd*, *J* = 6, 4, H–C(3′)); 4.55 (*s*, $PhCH_2$); 4.5–3.9 (*m*, 2 CH_3CH_2O, H–C(4′), H–C(5′), H–C(6′), H–C(2)); 3.67 (*dt*, *J* = 4, J(H,P) = 18, H–C(1)); 1.6–1.2 (*m*, 6 CH_3). ^{13}C-NMR: 137.9 (*s*); 128.3 (*d*); 127.70 (*d*); 126.66 (*d*); 112.3 (*s*); 109.0 (*s*); 99.2 (*dd*, *J*(C,P) = 10.6); 83.5 (*d*); 82.7 (*d*); 79.5 (*d*); 72.8 (*d*); 73.3 (*t*); 67.2 (*dt*, *J*(C,P) = 5.6); 66.8 (*t*); 62.6 (*dt*, *J*(C,P) = 6.9); 62.4 (*dt*, *J*(C,P) = 6.8); 60.4 (*dd*, *J*(C,P) = 151.6); 26.8 (*q*); 26.0 (*q*); 25.3 (*q*); 24.6 (*q*); 16.5–16.3 (*m*). ^{31}P–NMR: 24.1..

13b: R_f as **13a**. HPLC (conditions see **13a**): t_R 12.5 min. $[\alpha]_D^{25}$ = +13.4° (*c* = 1.1, $CHCl_3$). IR: 3550*w*, 3380*w* (very br.), 3090*w*, 3060*w*, 3030*w*, 2990*s*, 2938*w*, 2908*m*, 2870*w*, 2450*w* (br.), 1601*w*, 1490*w*, 1475*w*, 1451*m*, 1382*m*, 1371*m*, 1160*m*, 1110*m*, 1090*s*, 1065*s*, 1025*s*, 973*s*, ^{1}H-NMR: 7.4–7.3 (*m*, Ph); 6.29 (*s*, OH, exch. D_2O); 5.03 (*d*, *J* = 6.0, H–C(2′)); 4.96 (*s*, H–C(1′)); 4.83 (*dd*, *J* = 3.9, 5.9, H–C(3′)); 4.55 (*s*, $PhCH_2$); 4.35 (*ddd*, *J* = 5.3, 6.2, 7.8, H–C(5′)); 4.25–3.95 (*m*, 8 H); 3.95–3.75 (*m*, 2 H); 1.5–1.3 (*m*, 6 CH_3). ^{13}C-NMR: 138.0 (*s*); 128.5 (*d*); 127.8 (*d*); 112.4 (*s*); 109.2 (*s*); 97.6 (*dd*); 84.6 (*d*); 83.6 (*d*); 80.7 (*s*); 73.7 (*d*); 73.2 (*t*); 67.1 (*t*); 65.6 (*dt*, *J*(C,P) = 3.9); 62.7 (*dt*, *J*(C,P) = 2.9); 59.5 (*dd*, *J*(C,P) = 166.5); 27.0 (*s*); 26.3 (*s*); 25.5 (*s*); 24.8 (*s*); 16.6 (*s*); 16.5 (*s*). ^{31}P-NMR: 24.52.

Data of the crude mixture: HPLC (*Zorbax-Sil*, hexane/CH_2Cl_2/MeOH 80:20:1.5, 2 ml/min): **13a**: 11.24 min (13.8); **13b** 9.96 min (1.00). ^{31}P-NMR: **13a**: 24.09 (18.4); **13b**: 24.63 (1.00).

4.2. *With* t-*BuOK and* CH_2Cl_2. See *2.1*. Data of the crude mixture: ^{31}P-NMR: **13a**: 24.18 (4.50); **13b**: 24.54 (1.00).

4.3. *With* t-*BuOLi and THF*. See *2.2*. Data of the crude mixture: HPLC (*Zorbax-Sil*, hexane/CH_2Cl_2/MeOH 90:10:1, 2 ml/min): **13a**: 29.17 min (20.9); **13b**: 25.62 min (1.00). ^{31}P-NMR: **13a**: 23.95 (24.0); **13b**: 24.67 (1.00).

4.4. *With* t-*BuOK and THF*. See *2.2*. Data of the crude mixture: ^{31}P-NMR: **13a**: 23.98 (8.58); **13b**: 24.69 (1.00).

5. *Dibenzyl {(1S)- and (1R)-2-Benzyloxy-1-[*N*-(2,3:5,6-di-*O*-isopropylidene-α-*D*-mannofuranosyl)-*N*-hydroxyamino]ethyl}phosphonate* (**14a** and **14b**, resp.). 5.1. *With* t-*BuOLi and* CH_2Cl_2. See *2.1*. Dibenzyl phosphite (4.25 ml, 19.3 mmol), **11** (3.92 g, 9.6 mmol), CH_2Cl_2 (100 ml), and *t*-BuOLi (510 mg, 6.4 mmol). Chromatography of the crude product on silica gel (hexane/AcOEt 3:2, without separation of diastereoisomers) gave 5.91 g (92%) of **14a**/**14b**. Three recrystallisations from hexane/CH_2Cl_2 gave 4.08 g (63%, d.e. 98.7% by HPLC) of **14a**. Isomer **14b** was obtained by prep. HPLC (*Zorbax-Sil*, hexane/CH_2Cl_2/MeOH 80:20:1) of the mother liquor.

14a: M.p. 135°, R_f (CH_2Cl_2/MeOH 9:1) 0.31. HPCL (*Zorbax-Sil*, hexane/CH_2Cl_2/MeOH 20:20:3, 1.5 ml/min): t_R 9.7 min. $[\alpha]_D^{20}$ = +16.2° (*c* = 2.1, $CHCl_3$). IR: 3660*w*, 3555*w*, 3400*w* (br.), 3090*w*, 3060*w*, 3030*w*, 2990*s*, 2955*m*, 2935*m*, 2890*w*, 2460*w* (br.), 1955*w*, 1880*w*, 1810*w*, 1490*w*, 1451*m*, 1380*s*, 1370*s*, 1320*m*, 1305*w*, 1159*m*, 1113*m*, 1064*s*, 1145–990*s*, 916*m*, 908*m*. ^{1}H-NMR: 7.4–7.2 (*m*, 3 Ph); 6.38 (*s*, OH, exch. D_2O); 5.07 (*s*, H–C(1′)); 5.1–4.9 (*m*, 2 $PhCH_2OP$); 4.95 (*d*, *J* = 6, H–C(2′)); 4.78 (*dd*, *J* = 6, 3.5, H–C(3′)); 4.48 (*s*, $PhCH_2$); 4.37–4.26 (*m*, H–C(5′)), 4.21 (*dd*, *J* = 7.5, 3.5, H–C(4′)); 4.15–3.85 (*m*, H–C(6′), H–C(2)); 3.75 (*dt*, *J* = 5.5, *J*(H,P) = 18.1, H–C(1)); 1.42 (*s*, CH_3), 1.39 (*s*, CH_3); 1.36 (*s*, CH_3); 1.32 (*s*, CH_3). ^{13}C-NMR: 137.8 (*s*); 136.3 (*d*, *J*(C,P) = 6.1);

128.5–127.5 (*m*); 112.3 (*s*); 109.0 (*s*); 99.3 (*dd*, *J*(C,P) = 11), 84.4 (*d*); 83.6 (*d*); 80.5 (*d*); 73.6 (*d*); 73.3 (*t*); 67.9 (*dt*, *J*(C,P) = 6.8); 67.6 (*dt*, *J*(C,P) = 6.7); 67.2 (*dt*, *J*(C,P) = 5.8); 66.8 (*t*); 60.7 (*dd*, *J*(C,P) = 151.4); 26.8 (*q*); 26.0 (*q*); 25.3 (*q*); 24.6 (*q*). ^{31}P-NMR: 25.2. Anal. calc. for $C_{35}H_{44}NO_{10}P$ (669.71): C 62.77, H 6.62, N 2.09, P 4.63; found: C 62.50, H 6.39, N 2.01, P 4.45.

14b: R_f as **14a**. HPLC (conditions see **14a**): t_R 8.5 min. $[\alpha]_D^{20} = +18.4°$ (*c* = 2.4, $CHCl_3$). IR: 3660*w*, 3555*w*, 3400*w* (br.), 3090*w*, 3060*w*, 3030*w*, 2990*s*, 2935*m*, 2885*m*, 2460*w* (br.), 1955*w*, 1880*w* (br.), 1810*w*, 1490*w*, 1451*m*, 1380*s*, 1370*s*, 1305*w*, 1155*m*, 1110*s*, 1064*s*, 1045–990*s*, 916*m*. ^{1}H-NMR: 7.4–7.2 (*m*, 3 Ph); 6.29 (*s*, OH, exch. D_2O); 5.08–4.92 (*m*, H–C(1'), H–C(2'), 2 PhCH_2OP); 4.75 (*dd*, *J* = 6, 3.8, H–C(3')); 4.46 (*s*, PhCH_2); 4.32 (*ddd*, *J* = 7.5, 5.5, 5.5, H–C(5')); 4.15 (*dd*, *J* = 3.8, 7.5, H–C(4')); 4.12–3.90 (*m*, H–C(6'), H–C(2)); 3.90–3.71 (*m*, H–C(1)); 1.47 (*s*, CH_3); 1.38 (*s*, CH_3); 1.36 (*s*, CH_3); 1.33 (*s*, CH_3). *J*(H–C(1)/H–C(2)) = 0.65 (2-D *J*-resolved ^{1}H-NMR spectra (400 MHz)). ^{13}C-NMR: 137.6 (*s*); 136.1 (*d*, *J*(C,P) = 5.6); 136.0 (*d*, *J*(C,P) = 5); 128.8–127.6 (*m*); 112.3 (*s*); 109.0 (*s*); 97.2 (*dd*, *J*(C,P) = 15.2); 84.5 (*d*); 83.6 (*d*); 80.5 (*d*); 73.5 (*d*); 73.1 (*t*); 68.1 (*dt*, *J*(C,P) = 6.8); 67.9 (*dt*, *J*(C,P) = 6.6); 66.9 (*t*); 65.4 (*dt*, *J*(C,P) = 5.4); 59.8 (*dd*, *J*(C,P) = 165.5); 26.8 (*q*); 26.1 (*q*); 25.3 (*q*); 24.6 (*q*). ^{31}P-NMR: 25.6.

Data of the crude mixture: HPLC (*Zorbax-Sil*, hexane/CH_2Cl_2/MeOH 150:50:3, 1.5 ml/min): **14a**: 11.59 min (8.91); **14b**: 9.53 min (1.00). ^{31}P-NMR: **14a**: 25.12 (8.45); **14b** 25.67 (1.00).

5.2. *With* t-*BuOLi and THF*. See *2.2*. Data of the crude mixture: HPLC (*Zorbax-Sil*, hexane/CH_2Cl_2/MeOH 80:20:1, 1.5 ml/min): **14a**: 20.93 min (10.8), **14b**: 16.66 min (1.00). ^{31}P-NMR: **14a**: 25.09 (12.1); **14b**: 25.60 (1.00).

6. *Diisopropyl {(1S)- and (1R)-2-Benzyloxy-1-[*N*-(2,3:5,6-di-*O*-isopropylidene-α-*D*-mannofuranosyl)-*N*-hydroxyamino]ethyl}phosphonate* (**15a** and **15b**, resp.). 6.1. *With* t-*BuOLi*. See *2.3*. Diisopropyl phosphite (0.25 ml, 3 mmol), *t*-BuOLi (120 mg, 1.5 mmol), CH_2Cl_2 (20 ml), and **11** (814 mg, 2 mmol) in 1 ml CH_2Cl_2. Crystallisation of the crude product from Et_2O/hexane gave 631 mg (55.1%) of **15a**. Prep. HPLC of the mother liquor gave **15b** (conditions see **15a**, 14 ml/min).

15a: M.p. 126°, R_f (A) 0.42. HPLC (*Zorbax-Sil*, hexane/CH_2Cl_2/MeOH 50:50:1.5, 2 ml/min): t_R 8.5 min. $[\alpha]_D^{25} = +26.7°$ (*c* = 1.3, $CHCl_3$). IR: 3560*w*, 3400–3100*w*, 3090*w*, 3070*w*, 3035*w*, 2990*s*, 2940*m*, 2880*w*, 2460*w*, 1495*w*, 1467*w*, 1452*m*, 1382*s*, 1372*s*, 1160*m*, 1142*m*, 1100*s*, 1070*s*, 1000*s* (br.), 888*m*, 860*m*. ^{1}H-NMR: 7.4–7.3 (*m*, Ph); 6.15 (*s*, OH, exch. D_2O); 4.98 (*s*, H–C(1')); 4.97 (*d*, *J* = 4.6, H–C(2')); 4.81 (*dd*, *J* = 4.6, 6.5, H–C(3')); 4.8–4.6 (*m*, 2 $(CH_3)_2CH$); 4.15–3.94 (*m*, H–C(1), H–C(6')); 1.40–1.25 (*m*, 8 CH_3). ^{13}C-NMR: 138.0 (*s*); 128.5–127.5 (*m*); 112.2 (*s*); 109.9 (*s*); 99.1 (*dd*, *J*(C,P) = 10.9); 84.4 (*d*); 83.4 (*d*); 80.5 (*d*); 73.5 (*d*); 73.1 (*t*); 71.2 (*dd*, *J*(C,P) = 6.9); 71.0 (*dd*, *J*(C,P) = 7.2); 67.1 (*dt*, *J*(C,P) = 10.7); 66.8 (*t*); 60.8 (*dd*, *J*(C,P) = 154.4); 26.0–23.7 (*m*). ^{31}P-NMR: 22.0. Anal. calc. for $C_{27}H_{44}NO_{10}P$ (573.62): C 56.54, H 7.73, N 2.44, P 5.40; found: C 56.26, H 7.73, N 2.30, P 5.35.

15b: R_f as **15a**. HPLC (conditions see **15a**): t_R 7.6 min. $[\alpha]_D^{25} = +16.6°$ (*c* = 1.3, $CHCl_3$). IR: 3560*w*, 3380*w* (very br.), 3090*w*, 3060*w*, 3030*w*, 2990*s*, 2940*m*, 2880*m*, 2460*w*, 1605*w*, 1498*w*, 1468*m*, 1453*m*, 1382*s*, 1372*s*, 1160*m*, 1145*m*, 1100*s*, 1068*s*, 1000*s* (br.), 940*m*, 889*m*. ^{1}H-NMR: 7.4–7.2 (*m*, Ph); 6.4 (*s*, OH); 5.01 (*d*, *J* = 6.0, H–C(2')); 4.95 (*s*, H–C(1')); 4.80 (*dd*, *J* = 3.9, 6.0, H–C(3')); 4.71 (*ca. dq*, *J* = 6.5, 2 $(CH_3)_2CH$); 4.54 (*d*, *J* = 11.8, 1 H, PhCH_2); 4.49 (*d*, *J* = 11.8, 1 H, PhCH_2); 4.35 (*m*, H–C(5')); 4.22 (*dd*, *J* = 3.9, 7.7, H–C(4')); 4.05–3.95 (*m*, H–C(6'), H–C(2)); 3.80–3.70 (*m*, H–C(1), H–C(2)); 1.5–1.2 (*m*, 8 CH_3). ^{13}C-NMR: 137.7 (*s*), 128.3–127.5 (*m*); 112.1 (*s*); 109.0 (*s*); 97.3 (*dd*, *J*(C,P) = 16.0); 84.5 (*d*); 83.6 (*d*); 80.5 (*d*); 73.5 (*d*); 72.7 (*t*); 71.3 (*dd*, *J*(C,P) = 7.2); 71.2 (*dd*, *J*(C,P) = 7.0); 66.9 (*t*); 65.5 (*dt*, *J*(C,P) = 5.9); 59.9 (*dd*, *J*(C,P) = 167.1); 26.8–23.8 (*m*). ^{31}P-NMR: 23.0.

Data of the crude mixture: ^{31}P-NMR: **15a**: 22.00 (15.6); **15b**: 22.82 (1.00). Crude **15** was transformed to phosphoserine (+)-**19**, as indicated below.

6.2. *With* t-*BuOK*. See *2.3*. Data of the crude mixture: ^{31}P-NMR: **15a**: 22.2 (1.5 ± 0.4); **15b**: 22.8 (1.0).

7. *Di(*tert*-butyl) {(1S)-2-Benzyloxy-1-[*N*-(2,3:5,6-di-O-isopropylidene-α-D-mannofuranosyl)-N-hydroxyamino]ethyl}phosphonate* (**16a**). 7.1. *With* t-*BuOLi*. See *2.3*. Di(*tert*-butyl) phosphite (0.3 ml, 1.5 mmol), *t*-BuOLi (60 mg, 0.75 mmol), CH_2Cl_2 (5 ml), and **11** (306 mg, 0.75 mmol) in CH_2Cl_2 (1 ml). Crystallisation from hexane gave 310 mg (68%) of **16a** (diastereoisomerically pure by ^{31}P-NMR). M.p. 134–5° (dec.), R_f (CH_2Cl_2/MeOH 25:1) 0.18. $[\alpha]_D^{25} = +26.5°$ (*c* = 1.1, $CHCl_3$). IR: 3550*w*, 3450–3200*w*, 3090*w*, 3060*w*, 3035*w*, 2985*s*, 2948*m*, 2878*w*, 2460*w* (br.), 1490*w*, 1475*w*, 1451*m*, 1392*m*, 1381*s*, 1307*s*, 1160*s*, 1110*s*, 1067*s*, 1038*s*, 990*s* (br.), 918*m*, 888*m*, ^{1}H-NMR: 7.4–7.2 (*m*, Ph); 6.11 (*s*, OH); 5.05 (*s*, H–C(1')); 5.02 (*d*, *J* = 6.1, H–C(2')); 4.82 (*dd*, *J* = 3.5, 6.1, H–C(3')); 4.60 (*ca. d*, *J* = 12.1, 1 H, PhCH_2); 4.53 (*ca. d*, *J* = 12.1, 1 H, PhCH_2); 4.4–4.2 (*m*, 2 H); 4.1–3.9 (*m*, 3 H); 3.87 (*ddd*, *J* = 4.2, 10.6, *J*(H,P) = 10.6, H–C(2)); 3.55 (*ddd*, *J* = 4.2, 6.6, *J*(H,P) = 17.6, H–C(1)); 1.6–1.3 (*m*, 10CH_3). ^{13}C-NMR: 138.1 (*s*); 128.5–127.5 (*m*); 112.1 (*s*); 108.9 (*s*); 98.8 (*dd*, *J*(C,P) = 10.3); 84.4 (*d*); 83.5 (*d*); 80.5 (*d*); 73.6 (*d*); 73.1 (*t*); 67.7 (*dt*, *J*(C,P) = 6.3); 62.4 (*dd*, *J*(C,P) = 155.1); 30.5 (*dq*); 30.3 (*dq*); 26.8 (*q*); 26.0 (*q*); 25.3 (*q*) 24.6 (*q*). ^{31}P-NMR: 14.8. Anal. calc. for $C_{29}H_{48}NO_{10}P$ (601.67): C 57.89, H 8.04, N 2.33, P 5.15; found: C 58.18, H 8.22, N 2.25, P 5.31.

Data of the crude mixture: ^{31}P-NMR: **16a**: 14.76 (22.4); **16b**: 16.23 (1.00). Crude **16** was transformed to phosphoserine (+)-**19**, as indicated below.

7.2. *With* t-*BuOK*. See *2.3*. Data of the crude mixture: ^{31}P-NMR: **16a**: 14.8 (1.7 ± 0.1); **16b**: 16.3 (1.0)

8. *Diethyl {(1S)-1-[*N-*Acetoxy-*N-*(2,3:5,6-di-O-isopropylidene-α-*D-*mannofuranosyl)amino]-2-(benzyloxy)-ethyl}phosphonate* (**17**). A mixture containing **13a** (75 mg, 0.14 mmol), Ac_2O (0.3 ml, 2.7 mmol), Py (0.3 ml, 4 mmol), and 4-(*N,N'*-dimethylamino)pyridine (DMAP, 3 mg) was stirred at r.t. (2h). Evaporation and chromatography on silica gel (hexane/AcOEt/MeOH 18:18:1) gave **17** (68 mg, 85%) as an oil. R_f 0.24 (hexane/AcOEt/MeOH 18:18:1). $[\alpha]_D^{25} = +12.1°$ (*c* = 1.2, $CHCl_3$). IR: 3090*w*, 3060*w*, 3030*w*, 2990*s*, 2935*m*, 2910*m*, 2870*m*, 2460*w* (br.), 1772*s*, 1493*w*, 1475*w*, 1451*m*, 1445*m*, 1381*s*, 1370*s*, 1160*s*, 1120–1000*s*, 970*s*, 890*m*. ^{1}H-NMR: 7.40–7.25 (*m*, Ph); 5.25 (*s*, H–C(1')); 4.82 (*dd*, *J* = 3.4, 5.9, H–C(3')); 4.62 (*d*, *J* = 5.9, H–C(2')); 4.50 (*s*, PhCH_2); 4.4–3.8 (*m*, 11 H); 2.04 (*s*, AcO); 1.48 (*s*, CH_3); 1.38 (*s*, CH_3); 1.34 (*s*, CH_3); 1.4–1.2 (*m*, 3 CH_3). ^{13}C-NMR: 169.1 (*s*); 137.8 (*s*); 128.2 (*d*); 127.6 (*d*); 127.5 (*d*); 112.8 (*s*); 109.1 (*s*); 97.8 (*dd*, *J*(C,P) = 7.0); 83.3 (*d*); 82.4 (*d*); 80.4 (*d*); 73.1 (*d*); 72.9 (*d*); 66.9 (*dt*, *J*(C,P) = 7.0); 66.8 (*t*); 62.7 (*dt*, *J*(C,P) = 6.7); 61.8 (*dt*, *J*(C,P) = 6.8); 58.9 (*dd*, *J*(C,P) = 149.8); 26.6 (*q*); 26.0 (*q*); 25.3 (*q*); 24.8 (*q*); 19.1 (*q*); 16.4 (*dq*, *J*(C,P) = 5.3); 16.3 (*dq*, *J*(C,P) = 4.3). Anal. calc. for $C_{27}H_{42}NO_{11}P$ (587.60): C 55.19, H 7.20, N 2.38; found: C 54.97, H 7.34, N 2.21.

9. *(+)-(*S*)- and (−)-(*R*)-Dibenzyl [2-Benzyloxy-1-(hydroxyamino)ethyl]phosphonate* ((+)- and (−)-**18**, resp.). A soln. of **14a** (4.08 g, 6.1 mmol) in MeOH/conc. HCl 10:1 (50 ml) was stirred at r.t. for 2 h. The mixture was diluted with ice-water (50 ml), then with $CHCl_3$ (100 ml), and neutralized with sat. $NaHCO_3$ soln. Washing of the $CHCl_3$ soln. with ice-water (2 × 20 ml) gave, after normal workup, a residue which was crystallized twice from Et_2O/hexane to yield 1.99 g (76.3%) of colorless, crystalline (+)-**18**. Chromatography of the combined mother liquors on silica gel (hexane/CH_2Cl_2 1:1) afforded another 248 mg (9.5%).

(+)-**18**: M.p. 62°, R_f (A) 0.32. $[\alpha]_D^{25} = +5.9°$ (*c* = 1.1, $CHCl_3$). IR (KBr): 3260*s*, 3060*m*, 3025*m*, 2920*m*, 2870*m*, 2835*m*, 2785*w*, 1960*w*, 1880*w*, 1815*w*, 1600*w*, 1525*w*, 1496*m*, 1451*m*, 1425*w*, 1405*w*, 1389*w*, 1359*w*, 1315*w*, 1285*w*, 1246*s*, 1234*s*, 1214*s*, 1152*w*, 1122*s*, 1079*m*, 1040*s*, 1005*s*, 988*s*, 930*m*, 910*m*, 871*s*, 841*m*, 748*s*, 740*s*, 728*s*, 698*s*, 620*w*, 600*s*. ^{1}H-NMR: 7.4–7.2 (*m*, 3 Ph); 5.9 (br. *s*, NH); 5.15–4.95 (*m*, PhCH_2OP); 4.52 (*s*, PhCH_2); 3.95–3.75 (*m*, H–C(2)); 3.61 (*ddd*, *J* = 4.5, 6.5, *J*(H,P) = 16, H–C(1)); 1.9 (br. *s*, OH). ^{13}C-NMR: 137.6 (*s*); 136.2 (*d*, *J*(C,P) = 6.8); 128.5–127.5 (*m*); 73.3 (*t*); 67.73 (*dt*, *J*(C,P) = 3.7); 67.66 (*dt*, *J*(C,P) = 3.4); 65.5 (*dt*, *J*(C,P) = 3.4); 60.9 (*dd*, *J*(C,P) = 151.2). ^{31}P-NMR: 25.1. Anal. calc. for $C_{23}H_{26}NO_5P$ (427.44): C 64.63, H 6.13, N 3.28, P 7.25; found: C 64.39, H 5.92, N 3.10, P 7.51.

Isomer (−)-**18** was prepared in the same manner: $[\alpha]_D^{25} = -5.9°$ (*c* = 1.0, $CHCl_3$). M.p., R_f, IR, ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR as indicated for (+)-**18**.

10. *(+)-(*S*)-[1-Amino-2-hydroxyethyl]phosphonic Acid* ((+)-**19**). 10.1. *From the Dibenzyl Phosphonate (+)-***18**. A soln. of (+)-**18** (2 g, 4.68 mmol) in MeOH (50 ml) containing 10% Pd/C was hydrogenated at r.t. overnight. The mixture was diluted with H_2O, filtered through *Celite*, washed with $CHCl_3$ (3 × 20 ml), and taken to dryness. The residue was dissolved in H_2O. Lyophilization gave (+)-**19** as a colorless foam, that crystallised from MeOH to yield 507 mg (77%) of tiny needles. M.p. 210–212°, R_f (A) 0.3. $[\alpha]_D^{25} = +30°$ (*c* = 1, H_2O). IR (KBr): 3600–3200*s*, 3200–2000*s*, 1640*m*, 1610*m*, 1530*m*, 1460*m*, 1450*m*, 1440*m*, 1398*w*, 1357*w*, 1295*m*, 1253*m*, 1230*m*, 1164*s*, 1135*s*, 1040*s*, 970*m*, 920*s*, 875*m*, 860*m*, 760*m*, 685*m*. ^{1}H-NMR (D_2O, pH 3): 4.02 (*ddd*, *J* = 12.4, 4.0, *J*(H,P) = 5.5, H–C(2)); 3.78 (*ddd*, *J* = 13, 10, *J*(H,P) = 4.1, H–C(2)); 3.38 (*ddd*, *J* = 10, 4, *J*(H,P) = 14.2, H–C(1)). ^{13}C-NMR (D_2O, pH 3): 58.9 (*dt*, *J*(C,P) = 2.6), 51.4 (*dd*, *J*(C,P) = 138). ^{31}P-NMR (D_2O, pH 3): 10.5 (*ca. dt*, *J*(P,H–C(1)) = 14, both *J*(P,H–C(2)) ≈ 5). Anal. calc. for $C_2H_8NO_4P$ (141.06): C 17.03, H 5.72, N 9.93, P 21.96; found: C 17.30, H 5.70, N 9.72, P 21.64.

10.2. *From the Dibenzyl Phosphonate* **14**. A soln. of crude **14** (0.3 mmol) in 1N HCl/MeOH (2 ml) was stirred at r.t. for 2 h and concentrated. After hydrogenation and workup (see above) resulted 17 mg (40%) of (+)-**19**. $[\alpha]_D^{25} = +24.3°$ (*c* = 0.8, H_2O).

10.3. *From the Diethyl Phosphonate* **23**. 10.3.1. By the same procedure as indicated for (+)-**31**, **23** (1.00 g, 5.1 mmol) gave a viscous oil, which was chromatographed (H_2O) on *Dowex 50W* (H^+) to afford 650 mg (91%) of (+)-**19**. $[\alpha]_D^{25} = +26.4°$ (*c* = 1.1, H_2O).

10.3.2. A soln. of **23** (205 mg, 1.0 mmol) and $(CH_3)_3SiBr$ (1 ml, 8 mmol) was stirred at r.t. for 15 h, then concentrated to dryness, and dissolved in H_2O (1 h). Purification on *Dowex 50* (H^+) gave 98 mg (70%) of (+)-**19**. $[\alpha]_D = +28.0°$ (*c* = 2.6, H_2O).

10.4. *From the Crude Diisopropyl Phosphonate* **15**. Procedure as indicated in *10.5*. After hydrogenation, the crude product was boiled in conc. HCl (4 ml) for 20 min to give a dark brown oil, which was chromatographed twice on *Dowex 50* (H^+). From **15** obtained with *t*-BuOLi resulted 39 mg (55%) of (+)-**19**, $[\alpha]_D^{25} = +25.3°$ (*c* = 1.2, H_2O).

10.5. *From the Crude Di(*tert*-butyl) Phosphonate* **16**. A soln. of crude **16** (0.5 mmol) in 1N HCl/MeOH (2 ml) was stirred for 1 h, diluted with MeOH (6 ml), treated with $PdCl_2$ (50 mg), and hydrogenated for 18 h, followed by filtration, concentration and chromatography on *Dowex 50* (H^+). From **16** obtained with *t*-BuOLi resulted 45 mg (63%) of (+)-**19**, $[\alpha]_D^{25} = +26.0°$ ($c = 1.5$, H_2O). From **16a** (178 mg, 0.30 mmol) resulted 35 mg (86%) of (+)-**19**, $[\alpha]_D^{25} = +28°$ ($c = 1.4$, H_2O), crystallizing in contact with MeOH to give 33 mg (78%) of (+)-**19**, $[\alpha]_D^{25} = +30°$ ($c = 1.7$, H_2O).

11. *(+)-(S)-Diethyl 2-Benzyloxy-1-(hydroxyamino)ethylphosphonate* (**21**). A soln. of **13a** (36 g, 66 mmol) in MeOH/conc. HCl 10:1 (1 l) was stirred at 60° overnight. At 0°, NaOAc (50 g) was added and most of the solvent was evaporated. Addition of sat. $NaHCO_3$ soln., followed by extraction with $CHCl_3$ (3 × 500 ml) and washing with H_2O (2 × 500 ml) gave after usual workup 19 g (95%) of **21**. Filtration through silica gel (A) gave anal. pure product. R_f (A) 0.3, $[\alpha]_D^{25} = +4.0°$ ($c = 1.1$, $CHCl_3$). IR: 3660*w*, 3580*m*, 3280*m* (br.), 3090*w*, 3060*w*, 2995*s*, 2930*m*, 2910*m*, 2870*m*, 1600*w*, 1495*w*, 1475*w*, 1450*m*, 1445*w*, 1390*m*, 1365*m*, 1200*s* (br.), 1165*m*, 1100*w*, 1050*s*, 1025*s*, 970*s*. ^{1}H-NMR: 7.4–7.3 (*m*, Ph); 4.58 (*s*, PhCH_2); 4.17 (*m*, CH_3CH_2O); 4.0–3.7 (*m*, H–C(2)); 3.56 (*m*, H–C(1)); 1.31 (*t*, $J = 7.1$, CH_3CH_2O); 1.29 (*t*, $J = 7.0$, CH_3CH_2O). ^{13}C-NMR: 137.4 (*s*); 127.9 (*d*); 127.2 (*d*); 72.9 (*t*); 65.3 (*dt*, J(P,C) = 3.5); 62.0 (*t*); 61.8 (*t*); 60.2 (*dd*, J(C,P) = 150.7); 16.2 (*q*); 15.9 (*q*). Anal. calc. for $C_{13}H_{22}NO_5P$ (303.30): C 51.48, H 7.31, N 4.62, P 10.21; found: C 51.23, H 7.25, N 4.52, P 10.30.

12. *(+)-(S)-Diethyl [1-Amino-2-(benzyloxy)ethyl]phosphonate* (**22**). Isolated as a by-product from the hydrogenation of **21**. R_f ($CHCl_3$/MeOH 17.3) 0.66, $[\alpha]_D^{25} = +7.8°$ ($c = 1$, $CHCl_3$). IR: 3445*w* (br.), 3090*w*, 3080*w*, 2980*s*, 2930*m*, 2910*m*, 2865*m*, 1600*w* (br.), 1495*w*, 1475*w*, 1455*m*, 1445*m*, 1390*m*, 1160*m*, 1095*s*, 1050*s*, 1025*s*, 965*s*. ^{1}H-NMR (90 MHz): 7.35 (br. *s*, Ph); 4.55 (*s*, PhCH_2); 4.15 (*q*, $J = 7$,CH_3CH_2O); 3.95–3.75 (*m*, 2 H); 3.6–3.2 (*m*, H–C(2)); 1.68 (br. *s*, NH_2, exch. with D_2O); 1.28 (*t*, $J = 7$, CH_3CH_2O); 1.26 (*t*, $J = 7$, CH_3CH_2O).

13. *(+)-(S)-Diethyl (1-Amino-2-hydroxyethyl)phosphonate* (**23**). A soln. of **21** (15.2 g, 30 mmol) in EtOH (250 ml) was treated with 10% Pd/C (7.5 g), warmed to 60° and hydrogenated for 24 h. Filtration through *Celite* and concentration to dryness gave a grey oil, which was chromatographed on silica gel ($CHCl_3$/MeOH 17:3) to afford 6.6 g (33.5 mmol, 67%) of **23**. R_f ($CHCl_3$/MeOH 17:3) 0.3. $[\alpha]_D^{25} = +9.0°$ ($c = 1$, $CHCl_3$). IR: 3620*w*, 3400*w* (br.), 2950*s*, 2940*m*, 2910*m*, 1600*w* (br.), 1445*w*, 1390*m*, 1370*w*, 1160*m*, 1100*m*, 1050*s*, 1025*s*, 965*s*. ^{1}H-NMR: 4.25–4.05 (*m*, CH_3CH_2O); 3.85 (*ddd*, $J = 11.5, 4.5$, J(H,P) = 14.5, H–C(2)); 3.73 (*ddd*, $J = 11.5, 6.5$, J(H,P) = 8.5, H–C(2)); 3.25 (*ddd*, $J = 6.5, 4.5$, J(H,P) = 13, H–C(1)); 2.32 (br. *s*, OH, NH, exch. D_2O); 1.35 (*t*, $J = 7.1$, 2 CH_3CH_2O). ^{13}C-NMR: 62.3–62.0 (*m*); 50.7 (*dd*, J(C,P) = 146.8); 16.3 (*dq*, J(C,P) = 5.5). ^{31}P-NMR: 27.4. Anal. calc. for $C_6H_{16}NO_4P$ (197.17): C 36.55, H 8.18, N 7.10, P 15.71; found: C 36.32, H 8.42, N 7.00, P 15.45.

14. *(+)-(1S,2'S)-Diethyl [1-(3,3,3-Trifluoro-2-methoxy-2-phenylpropionamido)ethyl]phosphonate* (**24**). A soln. of **23** (50 mg, 30.1 μmol) in CH_2Cl_2 (2 ml) containing Et_3N (100 μl) and DMAP (1 mg) was treated at 0° with (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionylchloride (78 mg, 31 μmol) and stirred (0°) for 4 h. The mixture was taken up in CH_2Cl_2 (50 ml), washed with 0.1N HCl (2 × 10 ml) and H_2O (10 ml), worked up as usual, and chromatographed on silica gel (CH_2Cl_2/MeOH 49:1) to give 92 mg (74%) of anal. pure **24**. M.p. 93–94° (*t*-Bu)OMe/hexane), R_f (A) 0.54. $[\alpha]_D^{25} = +20.1°$ ($c = 1.2$, $CHCl_3$). IR: 3620*w*, 3410*m* (br.), 3100*w*, 3060*w*, 3030*w*, 2950*w*, 2915*w*, 2890*w*, 2850*w*, 2450*w* (br.), 1698*s*, 1509*s*, 1501*s*, 1450*m*, 1392*m*, 1370*w*, 1265*s*, 1167*s*, 1105*s*, 1080*w*, 1050*s*, 1025*s*, 978*m*, 951*m*. ^{1}H-NMR: 7.7–7.4 (*m*, Ph and NH); 4.54 (*dddd*, $J = 3.5, 4.5, 10$, J(H,P) = 17, H–C(1)); 4.3–3.7 (*m*, H–C(2), and 2 CH_3CH_2O); 3.43 (*s*, CH_3O); 2.96 (br. *s*, OH); 1.31 (*t*, $J = 7.3$, CH_3CH_2O); 1.19 (*t*, $J = 7.0$, CH_3CH_2O). ^{13}C-NMR: 166.0 (*d*, $J = 5$); 132.2 (*s*); 129.3 (*d*); 128.2 (*d*); 127.5 (*d*); 123.6 (*q*, J(C,F) = 289.8); 84.0 (*q*, J(C,F) = 26.4); 62.84 (*dt*, J(C,P) = 6.4); 62.76 (*dt*, J(C,P) = 6.8); 61.0 (*t*); 54.9 (*dq*, $J = 1.5$); 47.5 (*dd*, J(C,P) = 153.6); 16.3 (*t*); 16.1 (*t*). Anal. calc. for $C_{16}H_{23}F_3NOP$ (413.33): C 46.50, H 5.61, N 3.39, P 7.49; found: C 46.33, H 5.84, N 3.20, P 7.35.

15. *(+)-*N*-(2,3:5,6-Di-*O*-isopropylidene-α-*D*-mannofuranosyl)-(2-methylpropan)imine* N*-Oxide* (**25**). A soln. of **9** (13.7 g, 50 mmol) in $CHCl_3$ (200 ml) was treated sequentially with 2-methylpropanal (5 ml, 55 mmol), $TsOH \cdot H_2O$ (19 mg, 0.1 mmol), and $MgSO_4$ (13 g). The mixture was vigorously stirred at r.t. for 5 h, neutralized (2.5 g $NaHCO_3$), filtered, and taken to dryness in vacuo (2 h). Crystallisation from cyclohexane afforded 13.7 g (83%) of **25** as a relatively unstable solid (storage over KOH decreased decomposition). Recrystallisation from cyclohexane gave an anal. pure sample. M.p. 155–156°, R_f (A) 0.38. $[\alpha]_D^{29} = +49.3°$ ($c = 1.81$, $CHCl_3$). UV (cyclohexane): 246 (10150). IR: 2985*s*, 2935*m*, 2875*m*, 1587*w*, 1460*w*, 1430*w*, 1382*s*, 1372*s*, 1345*w*, 1290*w*, 1160*w*, 1115*s*, 1092*s*, 1065*s*, 992*w*, 970*w*, 940*w*, 887*w*. ^{1}H-NMR: 6.71 (*d*, $J = 7.4$, H–C(1)); 5.28 (*s*, H–C(1')); 5.26 (*d*, $J = 6.3$, H–C(2')); 4.99 (*dd*, $J = 6.3, 3.9$, H–C(3')); 4.65 (*dd*, $J = 7.2, 3.9$, H–C(4')); 4.40 (*m*, H–C(5')); 4.12 (*m*, H–C(6')); 3.17 (*m*, H–C(2)); 1.51 (*s*, CH_3); 1.45 (*s*, CH_3); 1.38 (*s*, CH_3); 1.36 (*s*, CH_3); 1.13 (*d*, $J = 7.0$, CH_3–C(2)); 1.11 (*d*, $J = 6.8$, H–C(3)). ^{13}C-NMR: 143.6 (*d*); 112.8 (*s*); 109.0 (*s*); 102.1 (*d*); 85.4 (*d*); 84.2 (*d*); 80.1 (*d*); 73.0 (*d*);

66.3 (*t*); 26.6 (*m*); 25.8 (*m*); 25.3 (*m*); 25.1 (*m*); 24.3 (*m*); 18.9 (*d*); 18.5 (*d*). Anal. calc. for $C_{16}H_{27}NO_6$ (329.40): C 58.34, H 8.26, N 4.25; found: C 58.58, H 8.23, N 4.17.

16. *Diethyl {(+)-(1S)- 1-[N-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-N-hydroxyamino]-2-methylpropyl}phosphonate* (**26**). Diethyl phosphite (17 ml, 145 mmol) was added under N_2 to a soln. of **25** (13.7 g, 41.7 mmol, freshly prepared) in CH_2Cl_2 (350 ml) at −70°. *t*-BuOLi (2.1 g, 28 mmol) was introduced at that temp. and the mixture was allowed to warm to −20° (2 h). The mixture was washed with ice water (2 × 120 ml) and worked up as usual. Crystallisation of the residue (cyclohexane) gave 11.7 g (25.0 mmol, 60%) of **26**. M.p. 149° (dec.), R_f (A) 0.33. $[\alpha]_D^{25} = +25.5°$ (*c* = 1.2, $CHCl_3$). IR: 3570*w*, 3280*w* (br.), 2985*s*, 2935*m*, 2905*m*, 2890*w*, 1500*w* (br.), 1372*s*, 1160*s*, 1115*m*, 1085*s*, 1060*s* (br.), 1025*s*, 968*s* br., 890*w*. ^{1}H-NMR: 6.39 (*s*, OH, exch. D_2O); 5.00 (*d*, *J* = 6, H–C(2')); 4.95 (*s*, H–C(1')); 4.80 (*dd*, *J* = 6, 3.8, H–C(3')); 4.35 (*dd*, both *J* = 6, H–C(5')); 4.14 (*m*, 2 CH_3CH_2O); 4.2–4.0 (*m*, H–C(6'), H–C(4')); 3.22 (*dd*, *J* = 6.2, *J*(H,P) = 17.5, H–C(1)); 2.25 (*m*, H–C(2)); 1.5–1.1 (*m*, 8 CH_3). ^{13}C-NMR: 112.1 (*s*); 108.9 (*s*); 98.0 (*dd*, *J*(C,P) = 2.9); 84.2 (*d*); 80.2 (*d*); 73.2 (*d*); 66.7 (*t*); 64.8 (*dd*, *J*(C,P) = 137.1); 61.9 (*dt*, *J*(C,P) = 6.5); 60.9 (*dt*, *J*(C,P) = 7.3); 28.6 (*dd*, *J*(C,P) = 5.0); 26.7 (*q*); 26.0 (*q*); 25.3 (*q*); 24.6 (*q*); 21.4 (*dq*, *J*(C,P) = 7.2); 20.8 (*dq*, *J*(C,P) = 7.2); 16.4 (*dq*, *J*(C,P) = 3.5); 16.2 (*dq*, *J*(C,P) = 4.3). ^{31}P-NMR: 27.5.

17. *Diethyl {(−)-(1S)-1-[N-Acetoxy-N-(2,3:5,6-di-O-isopropylidene-α-D-mannofuranosyl)amino]-2-methylpropyl}phosphonate* (**27**). A mixture containing **26** (1.0 g, 2.14 mmol), Ac_2O (2 ml), Py (2 ml), and DMAP (12 mg, 0.1 mmol) was stirred at r.t. for 4 h. Evaporation and crystallisation of the residue (hexane) gave 765 mg (72%) of **27**. Recrystallisation (2×, hexane) gave an anal. pure sample. M.p. 92–93°, R_f (A) 0.38. $[\alpha]_D^{25} = -2.5°$ (*c* = 2.1, $CHCl_3$). IR: 2985*s*, 2935*s*, 2905*m*, 2835*w*, 2460*w*, 1770*s*, 1476*w*, 1452*w*, 1447*w*, 1382*s*, 1371*s*, 1160*m*, 1120*m*, 1080*m*, 1060*s* (br.), 1023*s*, 1000*m*, 968*s*. ^{1}H-NMR: 5.34 (*s*, H–C(1')); 4.83 (*dd*, *J* = 5.8, 3.7, H–C(3')); 4.69 (*d*, *J* = 5.8, H–C(2')); 4.41 (*ddd*, all *J* = 6, H–C(5')); 4.3–3.9 (*m*, 7 H, 2 CH_2O, H–C(4'), H–C(6')); 3.27 (*dd*, *J* = 8, *J*(H,P) = 19.5, H–C(1)); 2.10 (*s*, AcO); 2.1–1.9 (*m*, H–C(2)); 1.5–1.2 (*m*, 6 CH_3); 1.08 (*d*, *J* = 6.7, H–C(3)); 1.06 (*d*, *J* = 6.8, H–C(4)). ^{13}C-NMR: 169.1 (*s*); 112.6 (*s*); 109.1 (*s*); 97.0 (*d*); 83.1 (*d*); 82.2 (*d*); 80.3 (*d*); 73.0 (*d*); 66.8 (*t*); 64.2 (*dd*, *J*(C,P) = 135.8); 61.7 (*dt*, *J*(C,P) = 6.7); 60.9 (*dt*, *J*(C,P) = 7.4); 28.7 (*dd*, *J*(C,P) = 5.1); 26.8 (*q*); 26.0 (*q*); 25.3 (*q*); 24.8 (*q*); 21.2 (*dq*, *J*(C,P) = 5.7); 20.8 (*dq*, *J*(C,P) = 9.1); 19.4 (*q*); 16.5 (*dq*, *J*(C,P) = 5.7); 16.4 (*dq*, *J*(C,P) = 5.9). ^{31}P-NMR: 25.1. Anal. calc. for $C_{22}H_{40}NO_9P$ (493.54): C 53.54, H 8.12, N 2.83, P 6.28; found: C 53.29, H 8.36, N 2.71, P 6.05.

18. *(S)-Diethyl (1-Hydroxyamino-2-methylpropyl)phosphonate* (**28**). A soln. of **26** (100 mg, 0.21 mmol) in MeOH/conc. HCl 10:1 (10 ml) was stirred at r.t. for 1.5 h. At 0°, NaOAc (1 g) was added, and most of the solvent was evaporated. H_2O (20 ml) and 10% $NaHCO_3$ soln. (15 ml) were added. Workup with CH_2Cl_2 (3 × 20 ml) gave 50 mg (quant.) of crude **28**, which partially decomposed on silica gel. R_f (CH_2Cl_2/MeOH 9:1) 0.53. IR: 3585*w*, 3300*w* (br.), 2990*s*, 2935*m*, 2920*m*, 2875*m*, 2470*w*, 1466*w*, 1457*w*, 1443*w*, 1390*w*, 1368*w*, 1151*m*, 1098*m*, 1050*s*, 1025*s*, 965*s*. ^{1}H-NMR: 5.6 (very br. *s*, 2 H, NHOH); 4.16 (*m*, 2 CH_3CH_2O); 3.03 (*dd*, *J* = 6.2, *J*(C,P) = 14.0, H–C(1)); 2.25 (*m*, H–C(2)); 1.34 (*t*, *J* = 7.1, 2 CH_3CH_2O); 1.10 (*dd*, both *J* = 6, H–C(3) and H–C(4)).

19. *(+)-(S)-Diethyl (1-Amino-2-methylpropyl)phosphonate* ((+)-**29**). Methanolysis of **26** (6.95 g, 14.9 mmol) as described above afforded crude **28**, which was immediately dissolved in EtOH (175 ml), treated with 2N HCl (45 ml) and hydrogenated over 10% Pd/C (650 mg) for 18 h. The mixture was filtered through *Celite* and concentrated to give a mobile oil, which was taken up in 2N HCl (100 ml) and washed with CH_2Cl_2 (3 × 50 ml). The aq. phase was basified (2N NaOH) to pH 10 and extracted with CH_2Cl_2 (3 × 100 ml). Normal workup yielded 2.93 g (94%) of (+)-**29**, which was used in the next step without further purification. A small quantity was purified on silica gel (CH_2Cl_2/MeOH 94:6). R_f (AcOEt/MeOH 4:1) 0.37. $[\alpha]_D^{25} = +0.4°$ (*c* = 1.7, $CHCl_3$). $[\alpha]_D^{28} = -6.8°$ (*c* = 1.7, H_2O, for **29** as hydrochloride)[12]. IR: 3400*w*, 2930*m*, 2910*m*, 2870*m*, 2470*w*, 1465*w*, 1442*w*, 1390*m*, 1369*w*, 1160*m*, 1095*m*, 1050*s*, 1030*s*, 960*s*. ^{1}H-NMR: 4.25–4.05 (*m*, 2 CH_3CH_2O); 3.0–2.7 (br. *s*, H–C(1)); 2.2–2.0 (*m*, H–C(2)); 1.34 (*t*, *J* = 7.0, 2 CH_3CH_2O); 1.06 (*d*, *J* = 7.6, H–C(3)); 1.02 (*d*, *J* = 7.0, H–C(4)).

20. *(±)-(RS)-Diethyl (1-Amino-2-methylpropyl)phosphonate* ((±)-**29**). A mixture of (±)-**31** (200 mg, 1.3 mmol) and PCl_5 (625 mg, 3 mmol) was, after the spontaneous reaction, heated to 60° for 5 min and then cooled to 0°. After addition of EtOH (1 ml), the mixture was warmed to r.t., diluted with H_2O (50 ml), washed with CH_2Cl_2 (2 × 15 ml), basified (2N NaOH) to pH 10 and extracted with CH_2Cl_2 (3 × 25 ml). Usual workup afforded (±)-**29** (76 mg, 27%). Anal. data (R_f, ^{1}H-NMR, and IR) as (+)-**29**.

21. *(1S,2'S)- and (1R,2'S)-Diethyl [2-Methyl-1-(3,3,3-trifluoro-2-methoxy-2-phenylpropionamido)propyl]-phosphonate* (**30a** and **30b**, resp.). **30a**: To a soln. of (+)-**29** (55 mg, 0.26 mmol), CH_2Cl_2 (2 ml) and Et_3N (0.1 ml)

[12]) (+)-**29** was dissolved in HCl and concentrated to dryness.

under N_2 was added (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride (86 mg, 0.34 mmol). The mixture was stirred at r.t. for 1 h, diluted with CH_2Cl_2 (50 ml), and washed with sat. $NaHCO_3$ soln. (2 × 10 ml) and H_2O (10 ml). Usual workup gave 97 mg (86.7%) of **30a**. Chromatography on silica gel (CH_2Cl_2/hexane/MeOH 10:10:1) gave an analytical sample. R_f (CH_2Cl_2/MeOH 97:3) 0.35. HPLC (*Zorbax Sil*, hexane/CH_2Cl_2/MeOH 44:5:1, 2 ml/min): **30a**: 7.65 min (278); **30b**: 6.95 min (1.0).

30a: $[\alpha]_D^{25}$ = +40.5° (*c* = 1.4, $CHCl_3$). IR: 3420*m*, 3060*w*, 3030*w*, 2990*s*, 2935*w*, 2915*w*, 2890*w*, 2850*w*, 2460*w* (br.), 1698*s*, 1505*s*, 1468*m*, 1450*m*, 1391*m*, 1370*w*, 1290*m*, 1165*s*, 1102*s*, 1079*m*, 1050*s*, 1024*s*, 970*s*. ^{1}H-NMR: 7.5 (br. *s*, 2 H, Ph); 7.4 (*m*, 3 H, Ph); 7.18 (br. *d*, *J* = 11, NH, no exch. D_2O within 48 h); 4.36 (*ddd*, *J* = 11, 4.2, *J*(H,P) = 17, H–C(1)); 4.2–4.0 (*m*, 2 CH_3CH_2O); 3.38 (*q*, *J*(C,F) = 1.2, CH_3O); 2.4–2.2 (*m*, H–C(2)); 1.28 (*t*, *J* = 7, CH_3CH_2O); 1.22 (*t*, *J* = 7, CH_3CH_2O); 1.06 (*d*, *J* = 7, 2 CH_3–C(2)). ^{13}C-NMR: 166.1 (*d*, *J* = 5.6); 131.9 (*s*); 129.4 (*d*); 128.4 (*d*); 127.9 (*d*); 123.8 (*q*, *J*(C,F) = 290); 83.9 (*q*, *J*(C,F) = 32); 62.5 (*dt*, *J*(C,P) = 6.3); 62.0 (*dt*, *J*(C,P) = 7.1); 54.9 (*q*); 50.0 (*dd*, *J*(C,P) = 152.3); 28.8 (*dd*, *J*(C,P) = 2.8); 20.7 (*q*); 20.4 (*q*); 17.7 (*dq*, *J*(C,P) = 4.4); 16.2 (*dq*, *J*(C,P) = 5.8). ^{31}P-NMR: 24.1.

By a similar procedure a 1:1 mixture **30a**/**30b** was obtained from (±)-**29**. R_f and IR identical with **30a**. HPLC (conditions see **30a**): **30a**: 7.65 min (1.00); **30b**: 6.95 min (1.00).

30a/**30b**: $[\alpha]_D^{25}$ = +9.7° (*c* = 1.4, $CHCl_3$). ^{1}H-NMR: 7.6 (br. *s*, 2 H, Ph); 7.4 (*m*, 3 H, Ph); 7.18 (*d*, *J* = 12, 0.5 H, NH); 6.85 (*d*, *J* = 12, 0.5 H, NH); 4.38 (*ddd*, *J* = 12, 5, *J*(H,P) = 20, H–C(1)); 4.25–4.0 (*m*, 2 CH_3CH_2O); 3.52 (*q*, *J*(C,F) = 1.5, 1.5 H, CH_3O); 3.38 (*q*, *J*(C,F) = 1.3, 1.5 H, CH_3O); 2.4–2.2 (*m*, H–C(2)); 1.33 (*t*, *J* = 7.5, 1.5 H, CH_3CH_2O); 1.32 (*t*, *J* = 7.1, 1.5 H, CH_3CH_2O); 1.28 (*t*, *J* = 7.1, 1.5 H, CH_3CH_2O); 1.22 (*t*, *J* = 7.1, 1.5 H, CH_3CH_2O); 1.06 (*d*, *J* = 6.8, 3 H, H–C(3), CH_3–C(2)); 0.95 (*d*, *J* = 6.7, 1.5 H, H–C(3)); 0.90 (*d*, *J* = 6.9, 1.5 H, CH_3–C(2)). ^{31}P-NMR: **30a**: 24.09 (1.12); **30b**: 24.02 (1.00). Anal. calc. for $C_{18}H_{27}F_3NO_5P$ (425.39): C 50.82, H 6.40, N 3.29, P 7.28; found: C 50.62, H 6.20, N 3.08, P 7.15.

By the same way, (+)-**29** (obtained from crude, non-crystallized **26**) was transformed to **30a**/**30b**. HPLC (conditions see **30a**): **30a**: 7.60 min (27.6); **30b**: 6.95 min (1.00). ^{1}H-NMR: **30a**: 3.38 (2.93 H, CH_3O); **30b**: 3.52 (0.061 H, CH_3O). ^{31}P-NMR: **30a**: 24.09 (34.8); **30b**: 24.02 (1.00).

22. *[(+)-(S)-1-Amino-2-methylpropyl]phosphonic Acid* (**31**). A soln. of (+)-**29** (2.93 g, 14 mmol) in conc. HCl (100 ml) was boiled under reflux for 15 h. Evaporation gave a residue, which was dissolved in H_2O and concentrated *in vacuo* (3 ×) to afford a viscous oil, which was taken up in H_2O and treated with EtOH to give crystalline (+)-**31** (1.95 g, 85% resp. to **26**). M.p. 273–278°, R_f (B) = 0.4. $[\alpha]_D^{25}$ = +2.1° (*c* = 1.9, H_2O). $[\alpha]_D^{25}$ = –0.8° (*c* = 2.0, 1N NaOH). IR (KBr): 3400*m* (br.), 3100*s* (br.), 3000–2500*s*, 1620*m*, 1525*m*, 1475*w*, 1460*w*, 1400*w*, 1375*w*, 1335*w*, 1235*s*, 1170*s*, 1115*m*, 1065*s*, 1040*s*, 940*m*, 840*w*, 820*w*, 725*w*. ^{1}H-NMR: 3.08 (*dd*, *J* = 6.3, *J*(H,P) = 14.0, H–C(1)); 2.4–2.1 (*m*, H–C(2)); 1.13 (*d*, *J* = 7.1, H–C(3)); 1.09 (*d*, *J* = 6.8, H–C(4)). ^{13}C-NMR: 55.2 (*dd*, *J*(C,P) = 141.5); 27.7 (*d*); 19.9 (*dq*, *J*(C,P) = 7); 18.0 (*dq*, *J*(C,P) = 6.4). ^{31}P-NMR (D_2O): 13.6. Anal. calc. for $C_4H_{12}NO_3P$ (153.12): C 31.38, H 7.90, N 9.15, P 20.23; found: C 31.56, H 8.03, N 8.90, P 19.95.

23. *{(1S,1'S)- and (1R,1'S)-2-Methyl-1-[3'-oxo-4',7',7'-trimethyl-2'-oxabicyclo[2.2.1]heptan-1-carboxamido]propyl}phosphonic Acid* (**32a** and **32b**, resp.). A soln. of (±)-**31** (50 mg, 0.33 mmol), Py (2 ml), and DMAP (122 mg, 1 mmol) was treated under N_2 with (–)-camphanoyl chloride (215 mg, 1.0 mmol). After stirring at r.t. overnight, MeOH (2 ml) was added (0.5 h) and concentrated to dryness to give crude **32**. ^{31}P-NMR (D_2O/MeOH 1:1): **32a** 20.28 (100.0); **32b** 20.12 (101.6).

By the same procedure, (+)-**31** (chromatographed on *Dowex 50W* (H^+) in H_2O) was treated with (–)-camphanoyl chloride. ^{31}P-NMR (D_2O/MeOH 1:1): **32a**: 20.41; **32b**: *ca.* 20.17 (no integration because of bad resoln.). Crude **32** was taken in aq. H_2SO_4 (50 ml, pH 3.4), washed with CH_2Cl_2 (3 × 25 ml), acidified with 1N H_2SO_4 to pH 0.2, and extracted with CH_2Cl_2 (9 × 25 ml) to get a mixture (188 mg) of **32** and camphanic acid. ^{31} P-NMR (D_2O/MeOH 4:1) **32a**: 23.00 (24); **32b**: 22.88 (1.0).

24. *Diethyl {(1S)- and (1R)-1-[N-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)-N-hydroxyamino]-ethyl}phosphonate* (**34a** and **34b**, resp.). A soln. of **9** (547 mg, 2 mmol) in $CHCl_3$ (5 ml) was sequentially treated with acetaldehyde (270 mg, 6 mmol), TsOH·H_2O (2 mg, 0.01 mmol), and $MgSO_4$ (5 g). The mixture was vigorously stirred at r.t. overnight, neutralized ($NaHCO_3$), filtered, and concentrated to dryness in high vacuum (15 min). The residue was taken up in CH_2Cl_2 (15 ml), cooled to –70° and treated with diethyl phosphite (0.8 ml, 6 mmol) and *t*-BuOLi (110 mg, 1.8 mmol). The mixture was allowed to warm to –20° (2 h), diluted with CH_2Cl_2 (150 ml), and washed with ice-water (30 ml). Normal workup gave a residue, which was chromatographed (without separation of diastereoisomers) on silica gel (hexane/AcOEt/MeOH 14:6:1) to yield 340 mg (41.6%) of **34a**/**34b**, as a clear oil. R_f (hexane/AcOEt/MeOH 14:6:1) 0.2. $[\alpha]_D^{25}$ = +34.3° (*c* = 1.9, $CHCl_3$). IR: 3670*w*, 3560*w*, 3500–3100*w*, 2990*s*, 2940*m*, 2910*m*, 1479*w*, 1452*w*, 1444*m*, 1382*s*, 1371*s*, 1230*s* (br.), 1106*s*, 1105*s*, 1070–1020*s*, 970*s* (br.), 888*m*.

^{1}H-NMR: 6.17 (*s*, OH, exch. D_2O); 5.03 (*d*, *J* = 6.3, H–C(2')); 4.85 (*dd*, *J* = 6.3, 3.4, H–C(3')); 4.81 (*s*, H–C(1')); 4.32–4.28 (*m*, H–C(6')); 4.2–4.0 (*m*, H–C(4'), H–C(5'), 2 CH_3CH_2O); 3.47 (*dq*, *J* = 7.4, *J*(H,P) = 17.8, H–C(1)); 2.0–1.3 (*m*, 7 CH_3). ^{13}C-NMR: 111.7 (*s*); 108.6 (*s*); 100.5 (*dd*, *J*(C,P) = 17.1); 84.4 (*d*); 84.2 (*d*); 80.5 (*d*); 73.6 (*d*); 66.5 (*t*); 62.3 (*dt*, *J*(C,P) = 19.2); 62.0 (*dt*, *J*(C,P) = 19.0); 56.2 (*dd*, *J*(C,P) = 163.8); 26.6 (*q*); 25.8 (*q*); 25.1 (*q*); 24.2 (*q*); 16.4 (*dq*, *J*(C,P) = 3.5); 16.1 (*dq*, *J*(C,P) = 3.6); 10.8 (*q*). ^{31}P-NMR: 26.5.

25. *(+)-(S)-Diethyl (1-Aminoethyl)phosphonate* ((+)-**36**). An ice-cooled soln. of **34a**/**34b** (204 mg, 0.55 mmol) in MeOH was treated dropwise with MeOH/conc. HCl 10:1 (1 ml) and stirred at 0° for 4 h. After addition of NaOAc (150 mg), AcOH (5 ml), H_2O (5 ml), and 10% Pd/C (100 mg), the mixture was hydrogenated overnight. The mixture was filtered through *Celite*, concentrated to an oil, diluted with H_2O (40 ml), acidified to pH 1 (2N HCl), washed with CH_2Cl_2 (3 × 10 ml), basified to pH 10 (2N NaOH) and extracted with CH_2Cl_2 (6 × 20 ml). Usual workup gave 50 mg (50%) of (+)-**36**. R_f (CH_2Cl_2/MeOH 93:7) 0.24. $[\alpha]_D^{25}$ = +7.3° (*c* = 1.3, $CHCl_3$). IR: 3665*w*, 3380*w*, 3040*w*, 2990*s*, 2940*m*, 2905*m*, 2870*m*, 2835*w*, 2470*w* (br.), 1590*w* (br.), 1478*w*, 1450*m*, 1442*m*, 1391*m*, 1378*m*, 1369*m*, 1275*m*, 1161*m*, 1110*m*, 1097*m*, 1040*s* (br.), 1020*s* (br.), 865*m*. ^{1}H-NMR: 4.2 (*m*, 2 CH_3CH_2O); 3.2 (br. *s*, H–C(1)); 1.8 (br. *s*, exch. D_2O, NH_2); 1.4–1.2 (*m*, 3 CH_3). ^{13}C-NMR (D_2O/HCl, pH 2): 64.9 (*dt*, *J*(C,P) = 7.2); 42.2 (*dd*, *J*(C,P) = 158.8); 15.7 (*dq*, *J*(C,P) = 5.1); 12.5 (*dq*, *J*(C,P) = 3.2).

26. *(+)-(S)-(1-Aminoethyl)phosphonic Acid* ((+)-**37**). By a similar procedure as indicated for (+)-**31**, 112 mg (620 μmol) of (+)-**36** gave 56 mg (72%) of (+)-**37**. M.p. 275°, R_f (B) 0.34. $[\alpha]_D^{25}$ = +16.0° (*c* = 1.13, 1N NaOH). IR (KBr): 3500–3200*s*, 1625*m*, 1605*m*, 1545*m*, 1455*w*, 1440*w*, 1390*w*, 1230*s*, 1175*s*, 1090*m*, 1045*s*, 920*s*, 810*m*, 700*s*. ^{1}H-NMR (D_2O/NaOD): 2.7–2.5 (*m*, H–C(1)); 1.16 (*dd*, *J* = 7.2, *J*(H,P) = 14.6, H–C(2)). ^{13}C-NMR (D_2O): 58.0 (*dd*, *J*(C,P) = 145.1); 14.5 (*q*). ^{31}P-NMR (D_2O): 14.9. Anal. calc. for $C_2H_8NO_3P$ (125.07): C 19.21, H 6.45, N 11.20, P 24.77; found: C 18.95, H 6.30, N 11.18, P 24.50.

27. *(1S,2'S)- and (1R,2'S)-Diethyl [1-(3,3,3,-Trifluoro-2-methoxy-2-phenylpropionamido)ethyl]phosphonate* (**38a** and **38b**, resp.). 27.1. (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride (126.3 mg, 0.5 mmol) was added under N_2 to a mixture of (+)-**36** (60.4 mg, 0.33 mmol), Py (2 ml), and DMAP (1 mg, 0.01 mmol). After 30 min, the mixture was diluted with CH_2Cl_2 (50 ml) and washed with 1N HCl (2 × 15 ml) and H_2O (15 ml). Usual workup gave a mixture (182 mg) of **38** and 3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid. Chromatography on silica gel (CH_2Cl_2/hexane/MeOH 60:40:3) gave 126 mg (96%) of **38a**/**38b**. R_f (CH_2Cl_2/hexane/MeOH 60:40:3) 0.22. HPLC (*Zorbax ODS*, MeOH/H_2O 55:45, 45°, 1.2 ml/min): **38a**: 18.05 min (23.9); **38b**: 20.25 min (1.00). $[\alpha]_D^{25}$ = +39.7° (*c* = 3.2, $CHCl_3$). IR: 3660*w*, 3410*m*, 3100*w*, 3060*w*, 3035*w*, 2990*s*, 2940*m*, 2910*w*, 2880*w*, 2845*w*, 2460*w* (br.), 1695*s*, 1505*s*, 1449*m*, 1391*m*, 1378*w*, 1369*m*, 1300*m*, 1270*s*, 1165*s*, 1109*s*, 1078*s*, 1050*s*, 1020*s*, 971*s*, 950*s*, 908*s*. ^{1}H-NMR: 7.54 (br. *s*, 2 H, Ph); 7.45–7.35 (*m*, 3 H, Ph); 7.08 (*d*, *J* = 9.5, NH); 4.51 (*ddq*, *J* = 7.5, 9.5, *J*(H,P) = 15.5, H–C(1)); 4.2–3.9 (*m*, 2 CH_3CH_2O); 3.48 (*q*, J(H,F) = 3, 0.15 H, CH_3O); 3.38 (*q*, *J*(H,F) = 3, 2.85 H, CH_3O); 1.6–1.1 (*m*, 2 CH_3CH_2O, 3 H–C(2)). ^{13}C-NMR: 165.4 (*d*, *J*(C,F) = 6.1); 131.9 (*s*); 129.4 (*d*); 128.3 (*d*); 127.7 (*d*); 123.6 (*q*, *J*(C,F) = 289.9); 83.9 (*q*, *J*(C,F) = 26.4); 62.5 (*dt*, *J*(C,P) = 6.5); 62.3 (*dt*, *J*(C,P) = 7.1); 54.6 (*dq*, *J*(C,F) = 1.9); 40.7 (*dd*, *J*(C,P) = 157.5); 16.1 (*dq*, *J*(C,P) = 5.9); 15.3 (*q*). ^{31}P-NMR: 25.2.

27.2. By a similar procedure, a 1:1 mixture **38a**/**38b** was obtained from (±)-**36**. M.p. 80° (CH_2Cl_2/hexane), R_f as **38a**. HPLC (conditions see *27.1*): **38a**: 18.24 min (100.0); **38b**: 20.00 min (100.1). $[\alpha]_D^{25}$ = +12.2° (*c* = 2.2, $CHCl_3$). IR: 3660*w*, 3410*m*, 3090*w*, 3060*w*, 3035*w*, 2990*s*, 2940*w*, 2910*w*, 2880*w*, 2850*w*, 2460*w* (br.), 1695*s*, 1505*s*, 1449*m*, 1391*w*, 1380*w*, 1369*w*, 1300*w*, 1270*s*, 1165*s*, 1103*s*, 1078*m*, 1050*s*, 1020*s*, 971*s*, 950*s*, 907*w*. ^{1}H-NMR: 7.55 (br. *s*, 2 H, Ph); 7.4–7.3 (*m*, 3 H, Ph); 7.10 (*d*, *J* = 9.5, 0.5 H, NH); 6.92 (*d*, *J* = 9.5, 0.5 H, NH); 4.53 (*ddq*, *J* = 7.5, 9.5, *J*(C,P) = 15.5, H–C(1)); 4.3–3.9 (*m*, 2 CH_3CH_2O); 3.49 (*q*, *J*(H,F) = 3, 1.5 H, CH_3O); 3.39 (*q*, *J*(H,F) = 3, 1.5 H, CH_3O); 1.6–1.1 (*m*, 2 CH_3CH_2O, 3 H–C(2)). ^{13}C-NMR: 165.7 (*d*, *J* = 5); 166.6 (*d*, *J* = 5); 129.5, 128.5, 127.9, 124.4, 123.7, (*q*, *J*(C,F) = 289.9); 123.8 (*q*, *J* = 289.7); 84.0 (*q*, *J* = 26.3); 62.7 (*d*, *J*(C,P) = 3.4); 62.6 (*d*, *J*(C,P) = 3.4); 62.5 (*d*,*J*(C,P) = 3.3); 62.3 (*d*, *J*(C,P) = 3.3); 55.0, 54.8, 40.9 (*d*, *J*(C,P) = 157.4); 40.8 (*d*, *J*(C,P) = 157.1); 16.3, 16.2, 15.4, 15.3. ^{31}P-NMR: 25.3. Anal. calc. for $C_{16}H_{23}F_3NO_5P$ (397.33): C 48.37, H 5.83, N 3.53, P 7.80; found: C 48.11, H 5.67, N 3.45, P 7.71.

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