Carbohydrates as Chiral Templates: Stereoselective Synthesis of (*R*)- and (*S*)-α-Aminophosphonic Acid Derivatives

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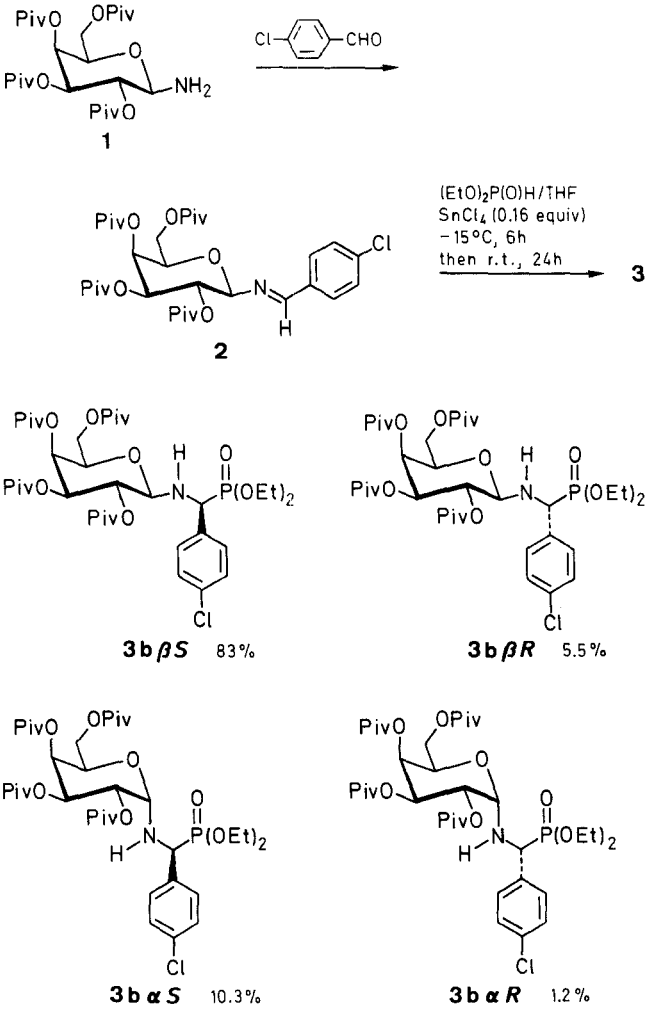
The stereoselective synthesis of diethyl (*S*)- or (*R*)-α-[(*O*-pivaloylhexapyranosyl)amino]benzylphosphonates is achieved via Lewis acid catalyzed addition of diethyl phosphite to *O*-pivaloylated *N*-benzylidene-β-D-galactosylamine or *N*-benzylidene-α-D-arabinopyranosylamine. The process can also be performed by a one-pot procedure selectively giving (*S*)-aminophosphonic acid derivatives from galactosylamine and (*R*)-aminophosphonic acid derivatives from β-L-fucosylamine as the chiral auxiliaries.

Due to their structural analogy to α-amino acids α-aminophosphonic acids and their derivatives are receiving increasing interest as substrates or inhibitors of enzymes involved in the metabolism of proteins and amino acids.[1] Several phosphonopeptides show antibiotic effects, others have been recognized as herbicides. According to these biological effects a number of asymmetric syntheses of α-aminophosphonic acid derivatives have been developed during the past two decades. The nucleophilic additions of phosphites to imines of α-methylbenzylamine[2] as well as the addition of a chiral phosphite to a cyclic imine[3] proceed with low or modest stereoselectivity. A partly high stereoselection was achieved by Vasella et al.,[4] who added phosphites to *N*-α-mannofuranosyl nitrones. In another type of syntheses, phosphonoglycine esters are used as the starting materials. The asymmetric hydrogenation of their *C*-alkylidene derivatives[5] is of limited applicability. The alkylation of carbanions either of camphor-derived imino derivatives of phosphonoglycine esters[6] or of *N*-acylphosphonoglycine ester amides formed from ephedrine[7] is more generally applicable and was achieved, in part, with high diastereoselection. The latter also holds true for aldol-type reactions between isocyanomethylphosphonates and aldehydes in the presence of an optically active gold complex with ferrocenyl alkylamine.[8] A further interesting concept consists in the reaction of electrophilic phosphonoglycine derivatives with *C*-nucleophiles, which allows the introduction of different side chains and, with chiral enamides, provides an efficient stereoselection.[9] We here report on an asymmetric synthesis of α-aminophosphonates in which *O*-pivaloylated glycosylamines[10] serve as the stereodifferentiating auxiliaries. By this method, both series of enantiomers of α-aminophosphonic acids can be obtained in partly high stereoselectivity. In many cases, recrystallization or flash chromatography allow the enrichment of the major diastereomer. Furthermore, the synthesis is also successful in an one-pot procedure without noticeable decrease of the asymmetric induction.

In the two-step procedure, the galactosylamine **1**[11] is reacted with 4-chlorobenzaldehyde to give the *N*-galactosylimine **2**. By catalyses with tin(IV) chloride (0.16 equiv) in tetrahydrofuran, the imine **2** reacts with diethyl phosphite to furnish the four diastereomeric *N*-galactosyl 4-chlorophenylphosphonoglycine esters **3a** in high yield. The reaction time can be reduced from 84 hours to 22 hours without changing the diastereomeric ratio of **3a** if 1.2 equiv of tin(IV) chloride are applied (Scheme 1).



Scheme 1

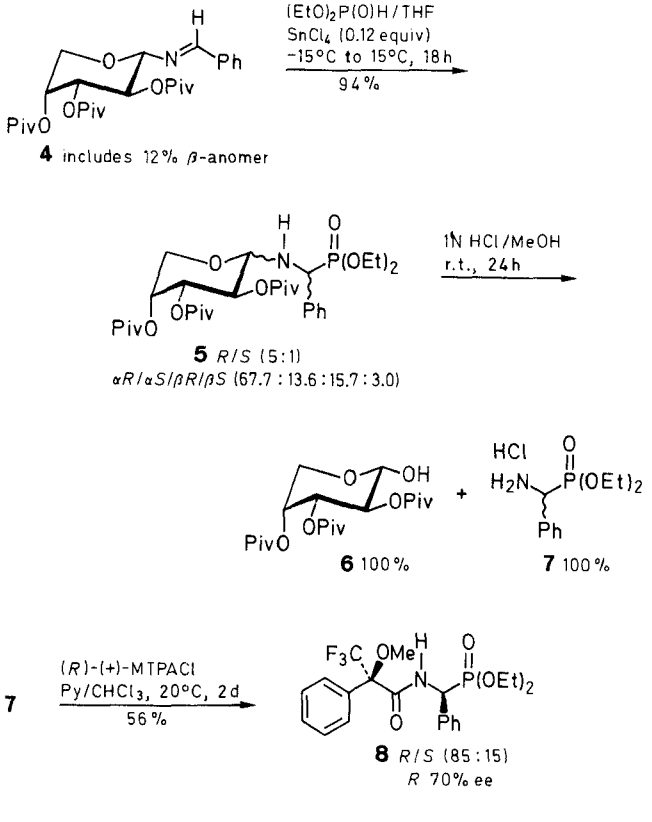
The ratio of diastereomers is determined by analytical HPLC. The anomeric configuration is assigned from the ^{13}C NMR signal of the anomeric carbon: $\delta = 85.2$ [**3a**(β*S*)]; 84.2 [**3a**(β*R*)]; 80.6 [**3a**(α*S*)].

Since tin(IV) chloride may cause anomerization either of the product **3a** or of the Schiff base **2**, the reaction pathway, on the one hand, can proceed via addition of the phosphite exclusively to the β-configurated imine **2**. This parallels the reaction of **2** with allylsilane.[12]

The minor α-anomers of **3a** then would arise from subsequent anomerization. On the other hand, a stereoselective addition of the phosphite to both anomers of the Schiff base could also occur. But, in this case, both anomers of **2** react with the same direction of asymmetric

induction as is shown below for the transformation of the *N*-benzylidene-α-D-arabinopyranosylamine **4**.[13]

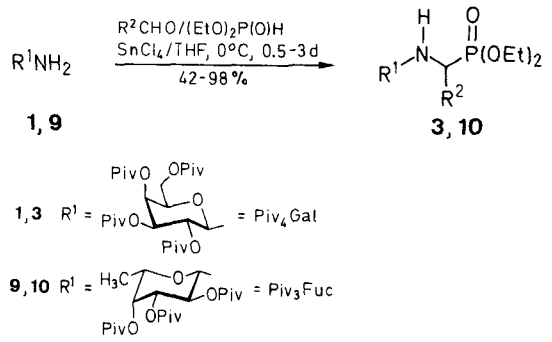
As has been demonstrated in Ugi reactions,[13] D-arabinopyranosylamine as the auxiliary induces the opposite chiral configuration in comparison to the D-galactosylamine. Therefore, its Schiff's bases, e.g., **4**, react with phosphite to form selectively (*R*)-aminophosphonates **5**, the analogues of L-amino acids (Scheme 2).



Scheme 2

The ratio of the obtained diastereomers **5** is practically independent from the content of the β-anomer of **4** (with axial imine!), which ranged from 6% to 39%. To assign the absolute configuration of the (arabinosylamino)phosphonate diastereomers **5**, the mixture **5** first is treated with 1 N hydrogen chloride in methanol at room temperature giving the easily separable carbohydrate template **6** and the α-aminobenzylphosphonate hydrochloride **7** in quantitative yield. The free base of **7** is transformed with some racemization to its *N*-benzyloxycarbonyl derivative whose optical rotation value $[[\alpha]_D^{22} + 6.2°$ (c = 1, $CHCl_3$)] compared with that reported in the literature[14] for the *R*-enantiomer $[[\alpha]_D^{22} + 14.0°$ (c = 2, MeOH)] confirms that the major diastereomers of **5** have (*R*)-aminophosphonate structure. To determine the enantiomeric excess of **7**, its amide **8** with Mosher's acid is formed by using pyridine as the scavenger of hydrogen chloride. The measured ratio of diastereomers of **8** (200 MHz, ^{1}H NMR) amounts to 85.2:14.8. This result is only in accord with the conclusion that either anomer of the imine **4** reacts with diethyl phosphite to preferably form to (*R*)-aminophosphonate **5αR** or **5βR**, respectively.

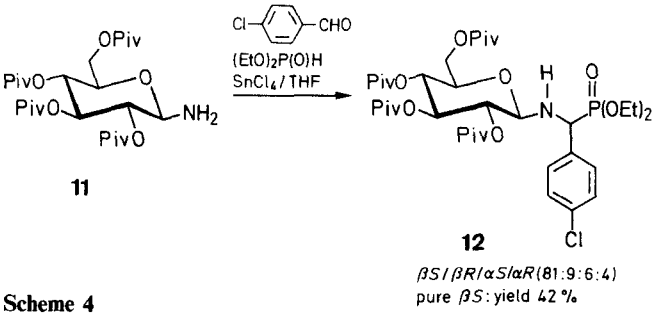
After the two-step reactions with isolated *N*-glycosylimines **2/4** have cleared the direction of asymmetric induction and the assignment of the configuration of the formed *N*-glycosylaminophosphonates, we have applied an one-pot synthesis of α-aminophosphonates, described by Kabachnik et al.,[15] to *O*-pivaloylated glycosylamines as, so to speak, asymmetric ammonia. In this sense, the galactosylamine or instead of the D-arabinosylamine,[13] the more strongly stereodifferentiating 2,3,4-tri-*O*-pivaloyl-β-L-fucopyranosylamine **(9)** are reacted with equivalent amounts of an aldehyde and 1.2 equivalents of each diethyl phosphite and tin(IV) chloride in tetrahydrofuran at 0 °C, (Scheme 3, Table 1) to deliver selectively the (*S*)-, **3**, or (*R*)-α-aminophosphonates **10**, respectively.



Scheme 3

After hydrolysis of the reaction mixture the ratios of diastereomers (Table 1) are determined by analytical HPLC directly from the crude product mixture. Then, unreacted amine, aldehyde and Schiff base are removed by flash-chromatography. The results given in Table 1 show that (*S*)-α-(galactosylamino)phosphonates **3** and (*R*)-α-(L-fucosylamino)phosphonates **10** are obtained in partly high yield **(3c,d,e,f, 10c,d,f)** and asymmetric induction **(3b,c,d, 10b,c,d)**. If one keeps in mind that the reactions are carried out in simple one-pot processes at relatively high temperature, their efficiency and stereoselectivity are astonishing. The reactivity of the corresponding aldehyde, that of its Schiff's base, as well as the tendency of the latter and the products themselves to undergo anomerizations, influence in a complex way the composition of the products **3/10**.

The efficiency of the method is increased by the observation, that the major diastereomer can crystallize from the solution of the diastereomeric mixture. So far, the best results in this sense are obtained with 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosylamine **(11)**. The α-(glucosylamino)benzylphosphonate **12** formed from **11** with 4-



Scheme 4

Table 1. Stereoselective Synthesis of (*S*)-**3** and (*R*)-α-Aminophosphonates **10** According to the One-Pot Procedure (Scheme 3)

Amine R^1	Aldehyde R^2	Time (d)	Product	Yield (%)	Ratio of Diastereomers				$[\alpha]_D^{22}$ ($c = 1$, $CHCl_3$)
					βS	βR	αS	αR	
Gal	4-ClC_6H_4	1	**3a**	67	79.1	10.5	5.9	4.5	+2.8
Fuc	4-ClC_6H_4	3	**10a**	50	12.4	78.2	2.2	7.2	+0.7
Gal	Ph	1	**3b**	50	89.5	7.1	2.3	1.1	−0.6
Fuc	Ph	1	**10b**	42	12.4	82.7	0.6	4.3	−15.7
Gal	4-MeC_6H_4	1	**3c**	78	91.0	6.2	2.0	0.8	+2.7
Fuc	4-MeC_6H_4	1	**10c**	81	9.8	85.1	1.2	3.9	−0.3
Gal	2-$MeOC_6H_4$	0.5	**3d**	80	54.7	0.8	43.2	1.3	+34.0
Fuc	2-$MeOC_6H_4$	0.5	**10d**	91	12.3	48.0	0.7	39.0	−38.4
Gal	Pr	2	**3e**	71	33.3	12.5	37.5	16.7	+30.9
Fuc	Pr	2	**10e**	46	6.0	46.0	12.0	36.0	−45.3
Gal	2-furyl	3	**3f**	89	69.2	16.2	11.0	3.6	+12.0
Fuc	2-furyl	3	**10f**	98	27.1	64.9	1.0	7.0	−14.0

Table 2. Analytical Data of Diethyl 1-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]alkylphosphonates **3**

Product	R^2	Molecular Formula[a]	Major Diastereomer 3βS		Minor Diastereomers	
			^1H NMR,[b] δ, J(Hz)	^{13}C NMR, δ	3βR	3αS
3a	4-ClC_6H_4	$C_{37}H_{59}ClNO_{12}P$ (775.5)	3.78 (dd, $J_{1,NH}$ = 12.4, $J_{1,2}$ = 8.8, 1-H), 4.51 (d, $J_{1',P}$ = 17.3, 1'-H)	54.83 (d,[c] C-1'), 85.28 (d,[d] C-1)	55.63 (C-1'), 84,53 (C-1)	54.08 (C-1'), 80.63 (C-1)
3b	Ph	$C_{37}H_{60}NO_{12}P$ (741.0)	3.77 (dd, $J_{1,NH}$ = 12.1, $J_{1,2}$ = 8.9, 1-H), 4.50 (d, $J_{1',P}$ = 17.1, 1'-H)	55.49 (d,[c] C-1'), 85.34 (d,[d] C-1)	56.24 (C-1'), 84.39 (C-1)	54.58 (C-1'), 80.63 (C-1)
3c	4-MeC_6H_4	$C_{38}H_{62}NO_{12}P$ (755.0)	3.80 (dd, $J_{1,NH}$ = 12.3, $J_{1,2}$ = 9.0, 1-H), 4.59 (d, $J_{1',P}$ = 16.5, 1'-H)	55.20 (d,[c] C-1'), 85.20 (d,[d] C-1)	56.15 (C-1'), 61.09 (C-6)	not detectable
3d	4-$MeOC_6H_4$	$C_{38}H_{62}NO_{13}P$ (771.0)	3.80 (dd, $J_{1,NH}$ = 11.1, $J_{1,2}$ = 9.0, 1-H), 5.12 (d, $J_{1',P}$ = 18.1, 1'-H)	47.22 (d,[c] C-1'), 86.14 (d,[d] C-1)	– 88.64 (C-1)	– 81.39 (C-1)
3e	Pr	$C_{34}H_{62}NO_{12}P$ (707.0)	3.78 (m, 1H, 1-H), 4.50 (m, 1H, 1'-H)	50.38 (d,[c] C-1'), 88.01 (d,[d] C-1)	55.20 (C-1'), 90.69 (C-1)	52.93 (C-1'), 82.81 (C-1)
3f	2-furyl	$C_{35}H_{58}NO_{13}P$ (731.0)	3.91 (dd, $J_{1,NH}$ = 11.1, $J_{1,2}$ = 6.8, 1-H), 4.62 (d, $J_{1',P}$ = 18.1, 1'-H)	50.06 (d,[c] C-1), 85.87 (d,[d] C-1')	49.91 (C-1'), 61.37 (C-6)	6.75 (C-6), 83.58 (C-1)

[a] Satisfactory elemental analyses obtained: C ±0.3, H ±0.25, N ±0.2.
[b] Numbering of carbohydrate atoms: 1,2,3..., phosphonic acid C, H: 1'...
[c] $^1J_{C',P}$ range between 150 Hz (**3e**) and 159 Hz (**3f**).
[d] $^3J_{C,P}$ range between 10.1 Hz (**3e**) and 17.0 Hz (**3c**).

Table 3. Analytical Data of Diethyl 1-[(2,3,4-Tri-*O*-pivaloyl-β-L-fucopyranosyl)amino]alkylphosphonates **10**

Product	R^2	mp (°C)	Molecular Formula[a]	Major Diastereomer 10βR		Minor Diastereomer	
				^1H NMR,[b] δ, J(Hz)	^{13}C NMR, δ	10βS	10αR
10a	4-ClC_6H_4	87–89	$C_{32}H_{51}ClNO_{10}P$ (675.5)	3.71 (dd, $J_{1,NH}$ = 11.8, $J_{1,2}$ = 9.1, 1-H), 4.54 (d, $J_{1',P}$ = 17.4, 1'-H)	54.87 (d,[c] C-1'), 85.01 (d,[d] C-1)	56.37 (C-1')	54.37
10b	Ph	oil	$C_{32}H_{52}NO_{10}P$ (641.0)	3.73 (dd, $J_{1,NH}$ = 9.7, $J_{1,2}$ = 9.0, 1-H), 4.56 (d, $J_{1',P}$ = 17.1, 1'-H)	55.52 (d,[c] C-1'), 85.05 (d,[d] C-1)	56.77 (C-1')	[e]
10c	4-MeC_6H_4	132	$C_{33}H_{54}NO_{10}P$ (655.0)	3.74 (dd, $J_{1,NH}$ = 11.1, $J_{1,2}$ = 9.7, 1-H), 4.54 (d, $J_{1',P}$ = 16.6, 1'-H)	55.29 (d,[c] C-1'), 84.98 (d,[d] C-1)	56.46 (C-1'), 84.72 (C-1)	[e]
10d	4-$MeOC_6H_4$	oil	$C_{33}H_{54}NO_{11}P$ (671.0)	3.87–4.16 [(m, 5H, 1-H, $P(OCH_2CH_3)_2$], 5.17 (d, $J_{1',P}$ = 17.7, 1'-H)	47.30 (d,[c] C-1'), 85.78 (d,[d] C-1)	68.09, 70.0, 71.06 (C-2, 3, 4, 5)	15.37 (C-6), 81.56 (C-1)
10e	Pr	oil	$C_{29}H_{54}NO_{10}P$ (607.8)	3.18 (m, 1H, 1-H), 3.96–4.14 [m, 5H, 1'-H, $P(OCH_2CH_3)_2$]	49.86 (d,[c] C-1'), 87.80 (d,[d] C-1)	18.78 (d, J = 12.4, C-3')	50.33 (C-1'), 82.81 (C-1)
10f	2-furyl	oil	$C_{30}H_{50}NO_{11}P$ (631.7)	3.99–4.15 [m, 5H, 1-H, $P(OCH_2CH_3)_2$], 4.65 (d, $J_{1',P}$ = 18.3, 1'-H)	50.13 (d,[c] C-1'), 85.61 (d,[d] C-1)	49.23 (C-1'), 84.09 (C-1)	50.48 (C-1'), 81.26 (C-1)

[a] Satisfactory elemental analyses obtained: C ±0.2, H ±0.2, N ±0.15.
[b] Numbering of carbohydrate atoms: 1,2,3..., phosphonic acid atoms: C1',2',3'...
[c] $^1J_{C,P}$ between 137.8 Hz (**10e**) and 158 Hz (**10f**).
[d] $^3J_{C,P}$ between 10 Hz (**10e**) and 16.9 Hz (**10c**).
[e] Not assigned.

chlorobenzaldehyde and diethyl phosphite is isolated after one recrystallization from light petroleum ether as almost pure (βS)-diastereomer. It appeared that also the (fucosylamino)phosphonates slowly crystallize while galactosyl derivatives could not be crystallized so far.

In conclusion, the described method offers a versatile way to both enantiomeric series of biologically interesting α-aminophosphonates. The synthesized compounds can easily be detached from the carbohydrate template which itself can be re-collected almost quantitatively.

TLC was carried out on silica gel 60 F_{254} (E. Merck, Darmstadt, Germany), detection with UV light (λ = 254 nm) and with 0.2% 3-methoxyphenol/2N H_2SO_4. For flash-chromatography silica gel (0.040–0.063 mm, E. Merck, Darmstadt, Germany) was used. Analytical HPLC was performed with an LKB equipment including a LKB 2140 Rapid Spectral Detector (diode array detection 190–370 nm) on Lichrospher 100 RP 18, 3 μ, 250 × 4 mm. Solvent was MeCN with 20% of H_2O, flow 1.0 mL/min.

400 MHz ^1H and 100.6 MHz ^{13}C NMR spectra were recorded on a Bruker AM-400 in $CDCl_3$ with TMS as internal standard. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Diethyl α-[(*O*-Pivaloylhexopyranosyl)amino]benzylphosphonates from *N*-Benzylideneglycosylamines; General Procedure:

To a solution of *N*-(4-chlorobenzylidene)-2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl amine (**2**;[16] 0.32 g, 0.5 mmol) or the analogously prepared *N*-benzylidene-2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine (**4**)[16,17] [mp 149 °C, $[\alpha]_D^{22}$ + 4.64° (*c* = 1, $CHCl_3$)] (0.25 g, 0.5 mmol) in dry THF (5 mL) at − 15 °C diethyl phosphite (0.08 mL, 0.6 mmol) and $SnCl_4$ (0.07 mL, 0.6 mmol) were subsequently added dropwise. After 6 h at − 15 °C and further 24 h at r.t. the mixture was hydrolyzed by addition of sat. aq $NaHCO_3$ (50 mL). The THF was evaporated in vacuo, and the remaining mixture was extracted with $CHCl_3$ (3 × 50 mL). The $CHCl_3$ solution was washed with sat. aq $NaHCO_3$ (50 mL), and dried ($MgSO_4$). After evaporation of the solvent the remaining residue was investigated by analytical HPLC. Purification by flash-chromatography on silica gel (80 g) using light petroleum ether/EtOAc 1) 4:1 v/v, 2) 1:2 v/v delivers the 1-(glycosylamino)alkylphosphonates **3a** or **5**, respectively.

Diethyl 4-Chloro-α-[2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino]benzylphosphonate (**3a**): Yield: 0.31 g (82%); mp 91–92 °C; $[\alpha]_D^{22}$ + 2.1° (*c* = 1, $CHCl_3$). Ratio of diastereomers (t_R, HPLC [min]): βS 85.4% (17.58), βR 4.5% (16.65), αS 8.6% (23.45), αR 1.5% (15.70).

$C_{37}H_{59}ClNO_{12}P$	calc.	C 57.25	H 7.61	N 1.81
(775.5)	found	57.47	7.67	1.84

3aβS: ^1H NMR ($CDCl_3$): δ = 1.04 [s, 9H, $C(CH_3)_3$], 1.13 [s, 9H, $C(CH_3)_3$], 1.17 [s, 9H, $C(CH_3)_3$], 1.02–1.22 [m, 6H, $P(OCH_2CH_3)_2$], 1.22 [s, 9H, $C(CH_3)_3$], 2.68 (dd, $J_{1,NH}$ = 12.4 Hz, $J_{P,NH}$ = 7.3 Hz, 1H, NH), 3.62 (dd, $J_{5,6b}$ = 7.4 Hz, $J_{5,6a}$ = 6.7 Hz, 1H, 5-H), 3.78 (dd, $J_{1,NH}$ = 12.4 Hz, $J_{1,2}$ = 8.8 Hz, 1H, 1-H), 3.88–4.06 [m, 6H, 6a-H, 6b-H, $P(OCH_2CH_3)_2$], 4.51 (d, $J_{1',P}$ = 17.3 Hz, 1H, 1'-H), 4.97 (dd, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 3.3 Hz, 1H, 3-H), 5.06 (dd, $J_{2,3}$ = 10.2 Hz, $J_{1,2}$ = 8.9 Hz, 1H, 2-H), 5.29 (dd, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 0.7, 1H, 4-H), 7.24–7.31 (m, 4H, Ph).

^{13}C NMR ($CDCl_3$): δ = 16.21 [d, $^3J_{C,P}$ = 4.3 Hz, $P(OCH_2CH_3)$], 16.25 [d, $^3J_{C,P}$ = 4.8 Hz, $P(OCH_2CH_3]$, 27.03, 27.13, 27.19 [$C(CH_3)_3$], 38.64, 38.76, 39.00 [$C(CH_3)_3$], 54.83 (d, $^1J_{C,P}$ = 152.6 Hz, C-1'), 61.53 (C-6), 62.83 [d, $^2J_{C,P}$ = 7.0 Hz, $P(OCH_2CH_3)$], 63.00 [d, $^2J_{C,P}$ = 6.8 Hz, $P(OCH_2CH_3)$], 67.21, 68.64, 71.34, 71.78 (C-2, C-3, C-4, C-5), 85.28 (d, $^3J_{C,P}$ = 16.7 Hz, C-1), 128.48 (d, $^4J_{C,P}$ = 2.1 Hz, C-3'', C-5''), 130.33 (d, $^3J_{C,P}$ = 5.6 Hz, C-2'', C-6''), 132.79 (d, $^2J_{C,P}$ = 8.6 Hz, C-1''), 133.98 (d, $^5J_{C,P}$ = 3.9 Hz, C-4''), 176.75, 177.01, 177.22, 177.71 (CO).

Signals of **3aβR**: δ = 55.63 (d, $^1J_{C,P}$ = 150.9 Hz, C-1'), 66.21, 67.70, 67.94, 68.29 (C-2, C-3, C-4, C-5), 84.53 (C-1), 129.39 (d, $^3J_{C,P}$ = 5.6 Hz, C-2'', C-6'').

Signals of **3aαS**: δ = 54.08 (d, $^1J_{C,P}$ = 161.0 Hz, C-1'), 66.36, 67.44, 67.98 (C-2, C-3, C-4, C-5), 80.63 (C-1), 129.84 (d, $^3J_{C,P}$ = 6.7 Hz, C-2'', C-6'').

Diethyl α-[(2,3,4-Tri-O-pivaloyl-α-D-arabinopyranosyl)amino]-benzylphosphonate (**5**): Yield: 0.31 g (94%), mp 95–97 °C, $[\alpha]_D^{22}$ − 33.8° (*c* = 1.00, $CHCl_3$).

$C_{31}H_{50}NO_{10}P$	calc.	C 59.33	H 7.98	N 2.23
(627.0)	found	59.34	7.94	2.04

Ratio of diastereomers (t_R MeCN, 30% H_2O, HPLC [min]): αR 67.7% (17.35), αS 13.6% (20.28), βR 15.7% (23.0); βS 3.0% (16.58).

5αR: ^1H NMR ($CDCl_3$): δ = 1.01 [s, 9H, $C(CH_3)_3$], 1.16 [m, 6H, $P(OCH_2CH_3)_2$], 1.19 [s, 9H, $C(CH_3)_3$], 1.21 [s, 9H, $C(CH_3)_3$], 2.67 (dd, $J_{1,NH}$ = 12.1 Hz, $J_{P,NH}$ = 7.1 Hz, 1H, NH), 3.30 (d, $J_{5a,5b}$ = 13.2 Hz, 1H, 5a-H), 3.70 (dd, $J_{1,NH}$ = 12.1 Hz, $J_{1,2}$ = 8.7 Hz, 1H, 1-H), 3.80 (dd, $J_{5a,5b}$ = 13.2 Hz, $J_{4,5b}$ = 2.2 Hz, 1H, 5b-H), 3.90–4.03 [m, 4H, $P(OCH_2CH_3)_2$], 4.52 (d, $J_{1',P}$ = 17.3 Hz, 1H, 1'-H), 4.93 (dd, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 6.5 Hz, 1H, 3-H), 5.03 ($J_{2,3}$ = 10.0 Hz, $J_{1,2}$ = 8.7 Hz, 1H, 2-H), 5.09 (d, $J_{3,4}$ = 6.5 Hz, 1H, 4-H), 7.24–7.39 (m, 5H, Ph).

^{13}C NMR ($CDCl_3$): δ = 16.17, 16.22 [$P(OCH_2CH_3)_2$], 26.97, 27.08, 27.16 [$C(CH_3)_3$], 38.62, 38.70, 38.84 [$C(CH_3)_3$], 55.45 (d, $^1J_{C,P}$ = 152.3 Hz, C-1'), 62.70 [d, $^2J_{C,P}$ = 7.8 Hz, $P(OCH_2CH_3)$], 62.78 [d, $^2J_{C,P}$ = 8.0 Hz, $P(OCH_2CH_3)$], 64.80 (C-5), 68.44, 68.92, 70.99 (C-2, C-3, C-4), 85.75 (d, $^3J_{C,P}$ = 16.7 Hz, C-1), 128.00 (C-4''), 128.15 (C-*m*), 129.11 (d, $^3J_{C,P}$ = 5.7 Hz, C-2'', C-6''), 134.15 (d, $^2J_{C,P}$ = 8.3 Hz, C-1''), 177.08, 177.23, 177.33 (CO).

Signals of **5αS**: δ = 55.95 (d, $^1J_{C,P}$ = 152.0 Hz, C-1'), 60.30 [d, $^2J_{C,P}$ = 12.3 Hz, $P(OCH_2CH_3)$], 62.21 [d, $^2J_{C,P}$ = 7.1 Hz, $P(OCH_2CH_3)$], 63.00 (C-5), 67.35, 67.50, 68.26 (C-2, C-3, C-4), 84.11 (C-1), 127.64 (C-*p*), 128.24 (C-*m*), 128.52 (d, $^3J_{C,P}$ = 9.5 Hz, C-2'', C-6'').

Signals of **5βR**: δ = 55.05 (d, $^1J_{C,P}$ = 152.0 Hz, C-1'), 81.00 (d, $^3J_{C,P}$ = 17.0 Hz, C-1).

Diethyl α-Aminobenzylphosphonate Hydrochloride (7):

The α-(arabinosylamino)benzylphosphonate **5** (0.25 g, 0.41 mmol) in MeOH (5 mL) was stirred with 1N HCl (0.62 mL) at r.t. for 24 h.

The MeOH was evaporated in vacuo, the remaining residue dissolved in 0.5N HCl (10 mL) and extracted with pentane (3 × 10 mL). The aqueous solution was evaporated to dryness to give **7** as colorless crystals, in quantitative yield, mp 164–165 °C; $[\alpha]_D^{22}$ − 2.4 (*c* = 1, H_2O).

From the pentane solution, after drying (Mg_2SO_4), and evaporation of the solvent, 2,3,4-tri-*O*-pivaloyl-α,β-D-arabinopyranose (**6**) was isolated in quantitative yield; mp 159 °C; $[\alpha]_D^{22}$ − 56.9° (*c* = 1, $CHCl_3$).

Diethyl α-[(Benzyloxycarbonyl)amino]benzylphosphonate:

This was prepared from **7** by treatment with equivalent amounts of 0.15 N NaOH and of benzyl chloroformate at 0 °C. After 2.5 h the colorless precipitate was dissolved in $CHCl_2$.

The CH_2Cl_2 solution was washed with sat. aq $NaHCO_3$, dried ($MgSO_4$) and evaporated in vacuo to give the benzyloxycarbonyl derivative of **7**. Yield: 55%, mp 134–135 °C; $[\alpha]_D^{22}$ + 6.2 (*c* = 1, $CHCl_3$) Lit.[14] $[\alpha]_D^{22}$ + 14.0° (*c* = 2, MeOH), corresponding to 42% ee in favor of the *R*-enantiomer.

$C_{19}H_{24}NO_5P$	calc.	C 60.49	H 6.37	N 3.71
(376.9)	found	60.47	6.60	3.50

The determined ee is lowered by the easy racemization occuring at phenyl phosphonoglycine esters. Therefore, the amide with Mosher's acid is synthesized:

Diethyl α-{(*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl]amino}-benzylphosphonate (8):
These diastereomers **8** were synthesized from the phenylphosphonoglycinate **7** (0.11 g, 0.39 mmol) in $CHCl_3$ (5 mL) with (*R*)-(+)-MTPACl (0.1 g, 0.4 mmol) in the presence of pyridine (0.5 mL). After 2 d at r.t., the solution was extracted with 2N HCl (15 mL) and sat. aq $NaHCO_3$ (15 mL). After drying ($MgSO_4$) the solvent was evaporated, the crude product was immediately investigated by ^1H NMR. Yield: 56%, colorless oil, t_R = 0.35 (light petroleum ether/EtOAc, 1:2, v/v).

^1H NMR ($CDCl_3$): δ = 1.06 [*t*, J_{vic} = 7.1 Hz, 3 H, $P(OCH_2CH_3)$], 1.17 [t, J_{vic} = 7.1 Hz, 3 H, $P(OCH_2CH_3)$], 3.36 (d, $^5J_{H,F}$ = 1.3 Hz, 3 H, OCH_3), 3.62–4.13 [m, 4 H, $P(OCH_2CH_3)_2$], 5.47 (dd, $^2J_{P,H}$ = 20.5 Hz, $J_{1,NH}$ = 9.8 Hz, 1 H, 1-H), 7.47 (m, 10 H, 2 Ph), 7.50–7.75 (m, 1 H, NH).

Signal of the minor *S*-diastereomer: δ = 3.47 (d, $^5J_{H,F}$ = 1.3 Hz, 3 H, OCH_3).

According to the ^1H NMR, the ratio of diastereomers **8** is 85.2:14.8, corresponding to an ee for **(R)-7** of 70.4%.

Diethyl 1-[(*O*-Pivaloylhexapyranosyl)amino]alkylphosphonates from Galactosylamine 1 or Fucosylamine 9; General Procedure:
To a solution of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine[16] (**1**, 0.5 mmol) or 2,3,4-tri-*O*-pivaloyl-β-L-fucopyranosylamine[17] (**9**; 0.5 mmol), respectively, and the corresponding aldehyde (0.5 mmol) in dry THF (5 mL), cooled to 0 °C, diethyl phosphite (0.08 mL, 0.6 mmol) and, subsequently, $SnCl_4$ (0.07 mL, 0.6 mmol) were added dropwise. Then, the ice-bath was removed. After the reaction was complete (TLC control), the mixture was carefully hydrolyzed by addition of sat. aq $NaHCO_3$ (50 mL). THF was evaporated in vacuo, and the remaining residue was extracted with CH_2Cl_2 (4 × 50 mL). The combined CH_2Cl_2 solutions were washed with sat. aq $NaHCO_3$ solution (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The obtained crude products **3/10** were investigated by analytical HPLC. Ratios of diastereomers were given in Table 1. The crude products were purified by flash-chromatography [light petroleum ether/EtOAc 1) 3:1 v/v, 2) 1:2 v/v] on silica gel (80 g). Yields and optical rotations, see Table 1. Further selected analytical data of the selectively formed (*S*)-1-(galactosylamino)alkylphosphonates **3** are given in Table 2, those of the (*R*)-1-(L-fucosylamino)alkylphosphonates **10** in Table 3.

For an example of detailed NMR data of 1-(galactosylamino)-alkylphosphonates **3**, see above the assignment for **3a**. As an example for the characterization of 1-(fucosylamino)alkylphosphonates **10**, the data of **10e** are given.

Diethyl 1-[2,3,4-Tri-O-pivaloyl-β-L-fucopyranosyl)amino]butylphosphonate **(10e):**

10eβR: ^1H NMR ($CDCl_3$): δ = 0.86 (m, 3 H, 4'-H), 0.94–1.23 [m, 6 H, $P(OCH_2CH_3)_2$], 1.07 [s, 9 H, $C(CH_3)_3$], 1.15 [s, 9 H, $C(CH_3)_3$], 1.19 (d, $J_{5,6}$ = 6.6 Hz, 3 H, 6-H), 1.23 [s, 9 H, $C(CH_3)_3$], 1.41–1.73 (m, 2'-H, 3'-H), 2.92 (br s, 1 H, NH), 3.18 (m, 1 H, 1-H), 3.69 (q, $J_{5,6}$) = 6.6 Hz, 1 H, 5-H), 3.96–4.14 [m, 5 H, 1'-H, $P(OCH_2CH_3)_2$], 5.04 (1 H, 2-H), 5.06 (dd, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 3.3 Hz, 1 H, 3-H), 5.17 (d, $J_{3,4}$ = 3.3 Hz, 1 H, 4-H).

^{13}C NMR ($CDCl_3$): δ = 13.62 (C-4'), 15.80 (C-6), 16.33 [d, $^3J_{C,P}$ = 6.9 Hz, $P(OCH_2CH_3)$], 16.41 [d, $^3J_{C,P}$ = 6.9 Hz, $P(OCH_2CH_3)$], 19.52 (d, $^3J_{C,P}$ = 6.9 Hz, C-3'), 27.04, 27.22, 27.25 [$C(CH_3)_3$], 32.96 (C-2'), 38.67, 38.75, 39.05 [$C(CH)_3$], 49.86 (d, $^1J_{C,P}$ = 137.8 Hz, C-1'), 61.95 [d, $^2J_{C,P}$ = 7.1 Hz, $P(OCH_2CH_3)$], 62.02 [d, $^2J_{C,P}$ = 7.1 Hz, $P(OCH_2CH_3)$], 63.76, 68.52, 69.91, 71.91 (C-2, C-3, C-4, C-5), 87.80 (d, $^3J_{C,P}$ = 10.1 Hz, C-1), 177.39, 177.42, 177.50 (CO).

Signals of **10eβS:** δ = 13.48 (C-4'), 16.07 (C-6), 18.78 (d, $^3J_{C,P}$) = 12.4 Hz, C-3'), 32.22 (C-2'), 63.66, 68.66, 69.06, 72.09 (C-2, C-3, C-4, C-5).

Signals of **10eαR:** δ = 13.98 (C-4'), 16.12 (C-6), 19.73 (d, $^3J_{C,P}$ = 12.4 Hz, C-3'), 32.92 (C-2'), 50.33 (d, $^1J_{C,P}$ = 149.8 Hz, C-1'), 61.61 [d, $^2J_{C,P}$ = 7.1 Hz, $P(OCH_2CH_3)$], 63.76, 67.54, 68.98, 71.05 (C-2, C-3, C-4, C-5), 82.81 (C-1).

Signals of **10eαS:** δ = 13.86 (C-4'), 16.21 (C-6), 18.78 (d, $^3J_{C,P}$ = 12.4 Hz, C-3'), 29.69 (C-2'), 63.66, 68.11, 69.74, 70.57 (C-2, C-3, C-4, C-5).

Diethyl 4-Chloro-α-[(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl)-amino]benzylphosphonate (12):
To ice-cold (0 °C) solution of 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosylamine[10,16] (**11**; 5.15 g, 10 mmol) and 4-chlorobenzaldehyde (1.41 g, 10 mmol) in THF (100 mL), diethyl phosphite (1.5 mL, 12 mmol) and, subsequently, $SnCl_4$ (1.4 mL, 12 mmol) were added dropwise. The mixture was allowed to warm to r.t. within 12 h. After 1 d diethyl phosphite (0.5 mL, 4 mmol) was added. The yellowish solution, after 3 d overall reaction time, was hydrolyzed by addition of sat. aq $NaHCO_3$ (200 mL), the THF was evaporated in vacuo, and the remaining solution extracted with $CHCl_3$ (4 × 100 mL). The $CHCl_3$ solution was washed with sat. aq $NaHCO_3$ (500 mL), dried ($MgSO_4$), and the solvent was evaporated in vacuo. The crude product **12** was investigated by analytical HPLC giving a ratio of diastereomers (t_R, HPLC [min]) of βS (24.27) 80.8%, βR (22.32) 8.8%, αS (18.92) 6.6%, βS (20.48) 3.8%. Flash-chromatography on silica gel using light petroleum ether/EtOAc [1.) 4:1 (v/v), 2.) 1:2 (v/v)] as the eluens gave **12** as colorless oil. Recrystallization of a sample (0.45 g) from light petroleum ether delivered a crystalline compound highly enriched of **12βS**: 0.27 g (42%); mp 119–120 °C; $[\alpha]_D^{22}$ −0.4 (*c* = 1, $CHCl_3$).

Ratio of diastereomers: **12βS**: 96.9%, **12βR**: 1.2%, **12αS**: 1.2%, **12αR**: 0.7%.

$C_{37}H_{59}ClNO_{12}P$	calc.	C 57.25	H 7.61	N 1.81
(775.5)	found	57.43	7.61	1.90

^1H NMR ($CDCl_3$): δ = 1.04 [s, 9 H, $C(CH_3)_3$], 1.05 [s, 9 H, $C(CH_3)_3$], 1.10–1.18 [m, 6 H, $P(OCH_2CH_3)_2$], 1.16 [s, 9 H, $C(CH_3)_3$], 1.19 [s, 9 H, $C(CH_3)_3$], 2.60 (dd, $J_{1,NH}$ = 12.3 Hz, $J_{P,NH}$ = 6.9 Hz, 1 H, NH), 3.36 (dd, $J_{5,6b}$ = 10.0 Hz, $J_{5,6a}$ = 5.7 Hz, 1 H, 5-H), 3.76 (dd, $J_{1,NH}$ = 12.2 Hz, $J_{1,2}$ = 9.4 Hz, 1 H, 1-H), 3.87–4.08 [m, 5 H, 6a-H, $P(OCH_2CH_3)_2$], 4.11 (d, $J_{6a,6b}$ = 12.2 Hz, 1 H, 4-H), 4.48 (d, $J_{1',P}$ = 17.4 Hz, 1 H, 1'-H), 4.89 (dd, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 9.2 Hz, 1 H, 4-H), 4.99 (dd, $J_{1,2}$ = 9.4 Hz, $J_{2,3}$ = 9.4 Hz, 1 H, 2-H), 5.17 (dd, $J_{2,3}$ = 9.4 Hz, $J_{3,4}$ = 9.4 Hz, 1 H, 3-H), 7.24–7.31 (m, 4 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 16.23 [d, $^3J_{C,P}$ = 5.0 Hz, $P(OCH_2CH_3)$], 16.27 [d, $^3J_{C,P}$ = 4.3 Hz, $P(OCH_2CH_3)$], 26.94, 27.09, 27.12, 27.19 [$C(CH_3)_3$], 38.60, 38.64, 38.73, 38.79 [$C(CH_3)_3$], 54.84 (d, $^1J_{C,P}$ = 152.8 Hz, C-1'), 62.17 (C-6), 62.87 [d, $^2J_{C,P}$ = 7.6 Hz, $P(OCH_2CH_3)$], 62.94 [d, $^2J_{C,P}$ = 6.9 Hz, $P(OCH_2CH_3)$], 68.34, 71.00, 72.61, 73.22 (C-2, C-3, C-4, C-5), 85.04 (d, $^3J_{C,P}$ = 16.7 Hz, C-1), 128.52 (C-3'', C-5''), 130.35 (d, $^3J_{C,P}$ = 6.1 Hz, C-2'', C-6''), 132.56 (d, $^2J_{C,P}$ = 8.5 Hz, C-1''), 134.05 (d, $^5J_{C,P}$ = 3.4 Hz, C-4''), 176.40, 176.89, 177.19, 177.87 (CO).

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