N-Monoalkylation of Tetra-*O*-benzyl-D-arabinonamide: Synthesis of Some Open-Chain Analogues of *N*-Acetylneuraminic Acid and Their Evaluation as Sialidase Inhibitors

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N-Arabinonoylglycine **2**, its phospho analogue (arabinonoylamino)methylphosphonate **14**, *N*-arabinonoyltaurine salt **18**, and [2-(arabinonoylamino)ethylidene]bis[phosphonic acid] **22** have been synthesized from D-arabinose in seven (**2** or **14**), and eight steps (**18** or **22a**), respectively. With the exception of the salt **22b**, none of these compounds showed a significant inhibitory activity *in vitro* against the sialidases of *Vibrio cholerae*, *Salmonella typhimurium*, or *Influenza A* (N9), or *B* (B/Lee/40) virus. Ammonolysis of the oxosulfonate **8** obtained by oxidation of the hydrogensulfite adduct **7** of 2,3,4,5-tetra-*O*-benzyl-*aldehydo*-D-arabinose (**6**) yielded the primary amide **9** (64% from **6**), which was alkylated with the triflates **10** or **11** of benzyl glycolate and dibenzyl hydroxymethylphosphonate, respectively, to give the protected *N*-arabinonoylglycinate **12** and the (arabinonoylamino)methylphosphonate **13** (45 and 90%, resp.). *N*-Alkylation of **9** with 2-bromoethyl triflate **15** followed by nucleophilic displacement with sodium sulfite yielded the protected taurine analogue **17** (21% from **9**), whereas the protected tetraethyl bis[phosphonate] **20** was formed in 90% yield by 1,4-addition of **9** to tetraethyl ethenylidenebis[phosphonate] **19**. Debenzylation of **12** and **13**, followed by purification by reversed-phase HPLC gave the triethylammonium salt of *N*-(D-arabinonoyl)glycine (**2**) and triethylammonium (D-arabinonoylamino)methylphosphonate (**14b**), respectively, whereas the deprotection of **17** afforded the *N*-(D-arabinonoyl)taurine salt **18**. Debenzylation of **20**, followed by treatment with Me_3SiBr and hydrolysis of the resulting silyl ester gave the bis[phosphonic acid] **22a** (3 steps, 88%).

1. Introduction. – In the context of the reported inhibitor activity of the δ-lactone **1** against several sialidases (B/Berkeley/3/69) [1], we became interested in the synthesis of the hydrolysis product **2**, derived from D-arabinonamide, and its analogues as potential inhibitors of the neuraminidases of *Vibrio cholerae* and *Salmonella typhimurium*. The activity of **1** is surprising, considering the absence of an acidic function in **1**, known to be important for the inhibitory activity [2] [3], and of the pyranoside ring in its hydrolysis product **2**, both structural elements characterizing the archetypical inhibitor **3** (DANA) [4] [5]. Indeed, the *Glaxo* group has reported the inactivity of **2** as inhibitor against *Influenza* sialidases [6]. The glycine derivative **2** was prepared by treating dicyclohexylcarbodiimide (DCC)-activated arabinonic acid with *tert*-butyl glycinate. Following a different strategy for the synthesis of **2**, *i.e.*, *N*-monoalkylation of the benzyl-protected arabinonamide **9** (*cf. Scheme 2*), we have developed a convenient large-scale preparation of this amide. In the following, we report the experimental details and the results of the inhibition of additional sialidases.

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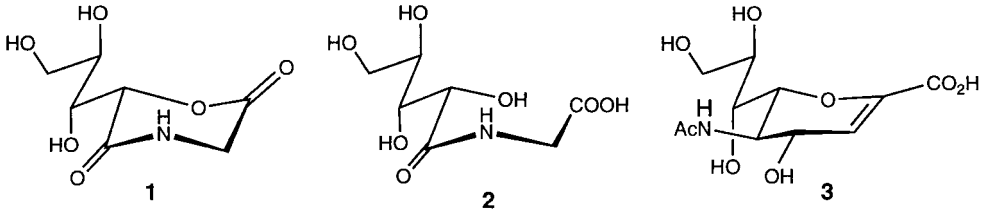
[1]) New address: *Novartis Pharma AG*, Chemical & Analytical Development, Process R&D, P. O. Box, CH-4002 Basel.



2. Results and Discussion. – Selective *N*-alkylations of carbohydrate-derived primary amides have not been reported to date. Examples of intermolecular mono-*N*-alkylations of primary amides are scarce, and most of them involve acidic amides, such as β-heteroaryl-amide [7], α-(trifluoromethyl)-β-aryl-amide [8], and trifluoro- or trichloroacetamides [9–11]. This may be due to the formation of mixtures by mono- and dialkylation [12] (*O*- and *N*-alkylation[2])), by epimerization in α-position [13] [18], and by β-elimination [18][19]. However, *N*-alkylation may be advantageous when the electrophile is readily accessible.

While attempts to perbenzylate potassium arabinonate led to mixtures, the benzylated arabinose dithioacetal **5** [20] was readily hydrolyzed to the aldehyde **6**[3]) (85% from the dithioacetal **4** [22]; see *Scheme 1*). Considering that 2,3,4,5,6-penta-*O*-benzylgluconoyl chloride cyclizes spontaneously to the corresponding 1,4-lactone [23], we avoided the preparation of an acyl chloride. The heavy-metal-free oxidation of aldehyde hydrogen sulfite adducts, described by *Wuts* and *Bergh* in 1986 [24] and apparently fallen into oblivion, appeared ideally suited for our needs. The resulting acyl sulfonates are mildly activated acyl derivatives that are readily transformed into esters or amides [24]. Indeed, tetra-*O*-benzyl-D-arabinonamide **9** is readily accessible on a preparative scale (> 30 g) by ammonolysis of the oxosulfonate **8** obtained by a *Pfitzner-Moffatt*-type oxidation of the hydrogen sulfite adduct **7** (64% over three steps, no purification of intermediates; *Scheme 1*).

The arabinonamide **9** was treated with BuLi at $-78°$, and monoalkylated with the triflate **10** [25] derived from benzyl glycolate to afford 45% of the glycine derivative **12**. The moderate yield reflects the instability of the triflate **10** under the basic reaction conditions. Similarly, mono-*N*-alkylation by **11** [26] derived from dibenzyl hydroxymethylphosphonate yielded 90% of the phosphonate **13**. No traces of α-epimerized, dialkylated, or elimination products could be detected in either case. Both **12** and **13** were smoothly hydrogenolysed to the *N*-arabinonoylglycine **2** and the isosteric (arabinonoylamino)methylphosphonate **14**, respectively (*Scheme 2*).

Efforts to synthesize the β-sulfonate analogue **18** by alkylation of **9** with sodium 2-bromoethanesulfonate failed under a range of conditions. The desired *N*-arabinonoyltaurine analogue **18a** was, however, obtained by nucleophilic substitution with sodium sulfite [27–29] of the *N*-(2-bromoethyl)arabinonamide **16**, followed by hydrogenolytic

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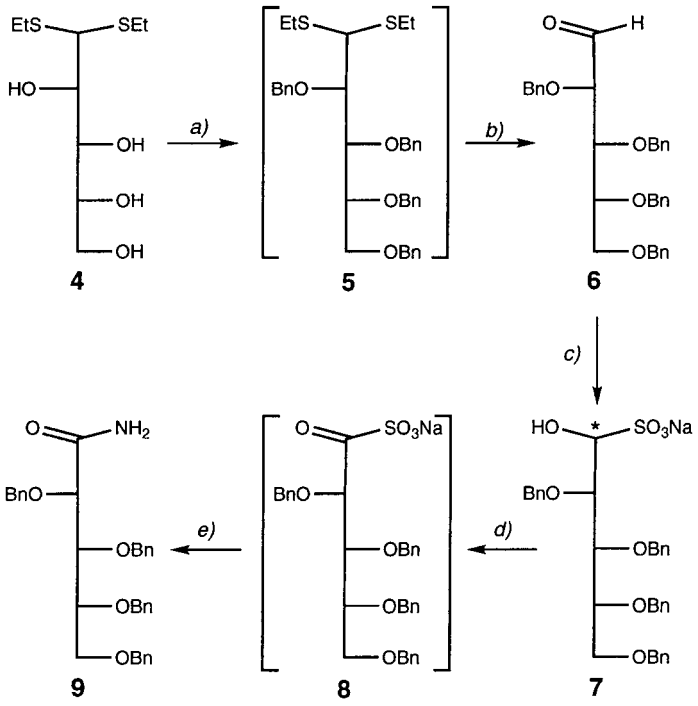
[2]) Sometimes α-*C*-alkylated products are obtained as well; for reviews, see [13] [14]. The ratio of *O*- *vs.* *N*-alkylated products is in many cases correctly predicted by *Gompper*'s rule [13] [15] [16]. For *N*-monoadditions of primary amides to vinyl ethers, yielding α-alkoxy- or α-(aryloxy)-methyl amides, *cf.* [17].

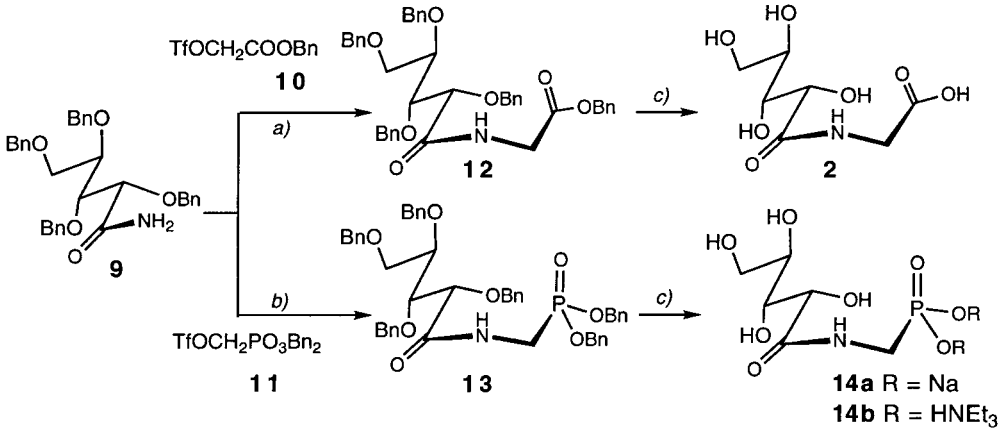
[3]) The aldehyde **6** has been reported by *Schreiber et al.* [21] who prepared it by a *de novo* synthesis. However, the reported specific rotation was $+2°$, while we found $+9.7°$ for a D-arabinose-derived sample (see *Exper. Part*).

Scheme 1



a) NaH, BnBr, Bn_4NI (0.05 equiv.), DMF, −20 to 25°; quant. *b*) $HgCl_2$, $CaCO_3$, $MeCN/H_2O$, 25°, 85%. *c*) NaOH, SO_2 (sat.), H_2O/Et_2O 3:5, 0–25°; quant. *d*) $DMSO/Ac_2O$, 25°, 24 h; quant. *e*) NH_3 (sat.), −4 to 38°; 64%.

Scheme 2

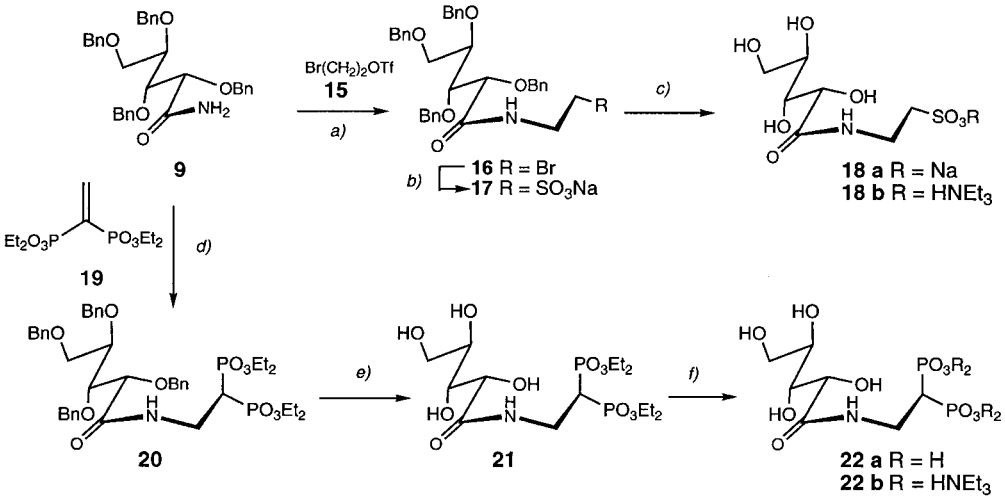


a) BuLi, 1.4 equiv. of $TfOCH_2COOBn$ (**10**), THF/DMPU 3:1, −85 to 20°; 45%. *b*) BuLi, 1.4 equiv. of $TfOCH_2PO_3Bn_2$ (**11**), THF/DMPU 3:1, −85 to 10°; 90%. *c*) H_2 (10 bar), 20% $Pd(OH)_2/C$, *t*-BuOH/H_2O 4:1, 25°; 91% of **2**, or 82% of **14a**.

debenzylation of the intermediate **17** (*Scheme 3*). The bromide **16** was prepared by monoalkylating **9** with excess 2-bromoethyl triflate[4]) (**15**) [30].

Finally, we synthesized the bis[phosphonate] **22** by mono-1,4-addition of **9**[5]) to tetraethyl ethenylidenebis[phosphonate] **19** [36–38]. Deprotection of the resulting **20**, first by hydrogenolysis to the tetrol **21** and then by transesterification with Me_3SiBr and hydrolysis of the silyl esters [35] [39–42] gave the bis[phosphonic acid] **22a** in 79% overall yield from **9** (*Scheme 3*).

Scheme 3



a) *t*-BuLi, 3.1 equiv. of $Br(CH_2)_2OTf$ (**15**), THF/DMPU 2:1, −78 to 25°; 42% of **16** and 43% of **9**. *b*) Na_2SO_3, $EtOH/H_2O$ 3:1, 80°; 50%. *c*) H_2 (10 bar), 20% $Pd(OH)_2/C$, *t*-BuOH/H_2O 4:1, 25°; 88%. *d*) *t*-BuOK, *t*-BuOH, 40–50°; 90%. *e*) H_2 (10 bar), 20% $Pd(OH)_2/C$, *t*-BuOH/H_2O 4:1, 25°; quant. *f*) 1. Me_3SiBr, CH_2Cl_2, −10 to 25°; 2. MeOH/H_2O 6:1, 25°; 88%.

Compounds **2**·NEt_3, **14b**, **18b**, and **22b** were tested against the sialidases of *Vibrio cholerae*, *Salmonella typhimurium* (LT2 strain), *Influenza A* (N2), and *Influenza B* (B/Lee/70) virus, with DANA (**3**) [4] [5] as a reference inhibitor and using the *Warren*-thiobarbituric acid assay [43–45][6]). Neither *N*-arabinonoylglycine **2** nor the isosteric phosphonate **14b** or the homologated sulfonate **18b** showed significant inhibition against any of the four sialidases tested. The homologated bis[phosphonate] **22b** showed a weak inhibition of the *Influenza B* enzyme (*Table*).

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4) Treatment of **9** with BuLi and only 1.2 equiv. of **15** led to the corresponding *N*-vinyl-amide (data not shown), isolated in low yields besides starting material.

5) For 1,4-additions to ethenylidenephosphonates, see [31–35].

6) We thank Prof. *Laver* (Influenza Research Unit, Australian National University, Canberra, Australia) for his help in establishing the assay and for generous gifts of *Influenza A* and *B*, and *S. typhimurium* sialidases.

Table. *Inhibition of Sialidases by* **2**·NEt_3, **14b**, **18b**, **22b**, *and* **3**. Enzyme activity in % of control at a uniform inhibitor concentration of $2.5 \cdot 10^{-3}$M.

Inhibitor	*V. cholerae*	*S. typhimurium*	*Influenza A*	*Influenza B*
2·NEt_3	not tested	not tested	100	100
14b	100	100	100	80
18b	90	100	90	100
22b	90	100	100	50
3	10	20	5	5

We thank the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG*, Basel, for financial support.

Experimental Part

1. *General.* Reagents were obtained in the best available commercial quality. Solvents for reactions and chromatography were distilled or dried according to standard procedures [46]. Molecular sieves were activated by heating at 200° for 48 h in high vacuum. Reactions involving alkyllithium were routinely conducted under Ar in flame-dried glasware [47]. TLC: *Merck* silica gel *60* precoated (F_{254}) aluminum plates; compound detection by treating with 'Mo-stain' soln. (400 ml of 10% H_2SO_4, 20 g $(NH_4)_6Mo_7O_{24} \cdot 6\,H_2O$, and 0.4 g of $Ce(SO_4)_2$), anisaldehyde stain (4 ml of anisaldehyde, 4 ml of conc. H_2SO_4, and 200 ml of AcOH) [48], or ninhydrin stain [48] (sat. ninhydrin soln. in EtOH) and heating at *ca.* 200°. Flash chromatography (FC): *Merck* silica gel 60 (40–63 μm). Anal. HPLC: *Merck-Hitachi*-system (HPLC Pump *L-6200 A, D-2500* Chromato-integrator); 4 × 250-mm columns; either refractometric (*Merck* differential refractometer *RI-71* or *LDC* anal. refracto-monitor *IV*) or UV detection (*Merck UV/VIS* detector *L-4250*; λ 254 nm). Prep. HPLC: *Dupont-8800* or *Merck-Hitachi* system (HPLC pump *L-6250*); 20 × 250-mm columns: refractometric (*Merck* differential refractometer *RI-71*) or UV detection (*Merck-Hitachi* UV detector *L-4000*). HPLC Columns: *RP-18* (anal.: *Merck LiChroSpher 100*, 5 μm; prep. *Merck Hibar LiChroSorb-RP 18*, 7 μm); *RP-8* (anal.: *Merck LiChroSpher 100*, 5 μm; prep.: *Merck Hibar LiChroSorb-RP 8*, 7 μm); CN (*Macherey-Nagel Nucleosil-5-CN*, 5 μm); NH_2 (anal.: Merck *LiChroSpher 100*, 5 μm; prep.: *Merck Hibar LiChroSorb-NH_2*, 7 μm); *SAX* (*Knauer SpheriSorb-SAX*, 5 μm), silica gel *60* (*Knauer SpheriSorb-SW*, 5 μm). M.p.: uncorrected; *Büchi 510* apparatus; in open capillaries. Optical-rotation values $[\alpha]_D^{25}$: *Perkin-Elmer 241* polarimeter, in a 1-dm cuvette. IR Spectra [cm^{-1}]: *Perkin-Elmer 297* spectrometer. NMR Spectra: *Varian-XL-200* spectrometer (^1H: 200 MHz, ^{13}C: 50 MHz, ^{31}P: 81 MHz); *Varian XL-300* spectrometer (^1H: 300 MHz, ^{13}C: 75 MHz, ^{31}P: 121.5 MHz); *Bruker-AMX-400* spectrometer (^1H: 400 MHz, ^{13}C: 100 MHz, ^{31}P: 162 MHz); *Bruker AMX-500* spectrometer (^1H: 500 MHz, ^{13}C: 125 MHz, ^{31}P: 202.5 MHz), and *Bruker AMX-600* spectrometer (^1H: 600 MHz, ^{13}C: 150 MHz, ^{31}P: 243 MHz); in deuterated solvents. δ Values in ppm relative to TMS as internal standard or external reference (solvent signal); for ^{31}P-NMR external reference H_3PO_4, coupling constants *J* (first order) in Hz; in ambiguous cases, assignments were secured by appropriately chosen 2D experiments, multiplicities by DEPT experiments; both ^{13}C- and ^{31}P-NMR spectra broadband-decoupled with respect to the ^1H nucleus. Mass spectra: *Varian MAT-112S* or *Finnigan MAT-90* (EI: 70 eV; CI: isobutane (C_4H_{10}) or NH_3 as carrier gas, ionized with 100–150 eV), *VG ZAB2-SEQ* (FAB: bombardment with 35-keV Cs-atoms (3-nitrobenzyl-alcohol, (NOBA) matrix), or *Finnigan TSQ 700* triple stage quadrupole spectrometer (ESI: *Analytica* ion source, *Brandford, Inc.*; N_2 as drying gas at 110°, 3.0–3.2 kV *U* at the electrospray probe); in (*m/z*) (rel. %). Elemental analyses were carried out by the Mikroanalytisches Laboratorium, Laboratorium für Organische Chemie, ETH Zürich.

2. *Syntheses. 2,3,4,5-Tetra*-O-*benzyl*-D-*arabinose* (**6**). Molecular sieves (3 Å; 10 g) were added to a soln. of D-*arabinose diethyl dithioacetal* **4** [22] (27.5 g, 107.25 mmol) in DMF (550 ml). Under cooling (ice bath), NaH (*Aldrich*, 95%; 14.44 g, 571.64 mmol) was added in portions under vigorous stirring. After the H_2 evolution had ceased, Bu_4NI (2.033 g, 5.50 mmol) was added, followed by dropwise addition of BnBr (55.9 ml, 471.94 mmol) in DMF (150 ml) within 100 min. Stirring was continued at 0° for 75 min. The mixture was kept at −25° for 12 h, warmed to r.t., and quenched by cautiously adding MeOH (50 ml), while stirring. After stirring for 2 h, the brown suspension was poured into a NH_4Cl/ice 1:1 (*ca.* 300 g). After addition of sat. aq. NaCl soln. (150 ml), the suspension was extracted with Et_2O (4 × 450 ml). The Et_2O phases were washed with sat. aq. NaCl soln. (4 × 150 ml) and H_2O (2 × 150 ml). The aq. phases were extracted with Et_2O (150 ml) and discarded. After drying ($MgSO_4$), the org. phases were taken to dryness under reduced pressure. Further drying in high vacuum (20 h): crude **5** [20] as yellow oil (59.5 g, 90%). A vigourously stirred soln. of this material in MeCN/H_2O 9:1 (800 ml)

was treated with $CaCO_3$ (48.27 g, 482.25 mmol). $HgCl_2$ (115.22 g, 424.39 mmol) was added in portions within 15 min. The resulting white suspension was stirred vigourously under Ar at r.t. for 22 h. After suction-filtration through a sand/*Celite*/sand bed, the clear filtrate was concentrated *i.v.* ($T \leq 30°$) to a turbid, yellowish soln. The filter cake was washed with AcOEt (5×300 ml) and the filtrate added to the concentrated suspension, which was then washed consecutively with 1M aq. KI (5×180 ml) ($\rightarrow$ org. phase turned lemon-yellow), 30% aq. $Na_2S_2O_3$ soln. (2×200 ml), and sat. aq. NaCl soln. (200 ml). The aq. phases were extracted with AcOEt ($2 \times$ 120 ml). The combined org. phases were dried (Na_2SO_4), evaporated, and the residue was further dried (24 h) at under high vacuum at 0° to yield a yellow oil (163.4 g) that was purified by FC (hexane/AcOEt 6:1 $\rightarrow$1:1): **6** as a slightly yellow honey (41.78 g, 85% over two steps). An anal. sample was obtained by HPLC (hexane/AcOEt 10:1, flow: 16 ml/min, detectionat 254 nm, t_R 11.2 min). R_f (hexane/AcOEt 6:1) 0.32. R_f (toluene/AcOEt 5:1) 0.80. $[\alpha]_D^{21} = -9.7$ ($c = 1.092$, $CHCl_3$) ([21] $[\alpha]_D = -2.1$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3060/3020/3000*w*, 2940/2910*w*, 2860*w-m*, 1725*s*, 1492*m-s*, 1450/1360/1330/1250*m*, 1095/1075v*s*, 1025*s*, 695*s*. ^{1}H-NMR (500 MHz, C_6D_6): 3.64 (*dd*, $^2J(5,5') = 10.6$, $^3J(5,4) = 4.5$ H–C(5)); 3.71 (*dd*, $^2J(5',5) = 10.6$, $^3J(5',4) = 3.0$, H′–C(5)); 3.88 (not fully resolved, *ddd*, H–C(4)); 4.06 (*dd*, $^3J(2,1) = 1.7$, $^3J(2,3) = 4.0$, H–C(2)); 4.21 (*dd*, $^3J(3,2) \approx 3.6$, $^3J(3,4) \approx$ 6.9, H–C(3)); 4.20–4.35 (*m*, 4H, PhCH_2); 4.47–4.58 (*m*, 4H, PhCH_2); 7.02–7.33 (*m*, 20 arom. H); 9.66 (*d*, $^3J(1,2) = 1.7$, H–C(1)). ^{13}C-NMR (125 MHz, C_6D_6): 69.21 (*t*, C(5)); 72.21, 73.25, 73.44, 74.19 (4 *t*, PhCH_2); 78.27 (*d*, C(4)); 79.42 (*d*, C(3)); 85.03 (*d*, C(2)); 127.73, 127.75, 127.98, 128.53, 128.55, 128.60, 128.61 (7*d*, arom. C); 138.20, 138.70, 138.94, 139.02 (4 *s*, C_{ipso}(Ph)); 201.27 (*s*, C(1)). CI-MS (NH_3): 530(7), 529(35, $[M+2+NH_3]^+$), 528(100, $[M+1+NH_3]^+$), 421($[M+2+NH_3-BnOH]^+$), 420(63, $[M+1+NH_3-BnOH]^+$), 403(10).

2,3,4,5-Tetra-O-*benzyl*-D-*arabinonamide* (**9**). SO_2 Gas was passed at 0° through a soln. of NaOH (20.0 g, 0.500 mol) in H_2O (150 ml) until the pH dropped to 7.0–6.5. A soln. of **6** (32.544 g, 63.73 mmol) in Et_2O (250 ml) was added dropwise at 0° under vigorous stirring. The ice bath was removed after 1 h. Stirring was continued at r.t. for 63 h (TLC monitoring). Then, the aq. phase was extracted with Et_2O (3×50 ml). The combined Et_2O phases were washed with H_2O dest. (50 ml), dried (Na_2SO_4), and evaporated. The residual yellow oil was co-evaporated with dry benzene (3×100 ml) and dried under high vacuum for 24 h: **7** (36.378 g, 93%) as a solid, yellow foam. The foam was taken up in dry CH_2Cl_2 (250 ml) and evaporated, and the residue dried (37–40°, 0.05 Torr) for *ca.* 18 h. A soln. of this material in abs. DMSO (250 ml) under Ar was stirred in an ice-bath. Ac_2O (44 ml, 465.5 mmol) was injected through a septum, and the resulting soln. was stirred at r.t. for 24 h. The resulting soln. of **8** was cooled to −4° and diluted with dry MeCN (150 ml). Dry NH_3 was bubbled through the turbid soln. for *ca.* 30 min (*Caution: strongly exothermic reaction*!). The temp. of the yellow soln. reached +38°. Stirring and cooling were continued until the temp. fell to 15–18°. The soln. was poured onto NH_4Cl/ice 1:1 (*ca.* 500 g). The pH was immediately adjusted to 6.5–7.0 with dil. AcOH. Extraction with Et_2O (5×300 ml). The combined org. phases were washed with sat. aq. NaCl soln. (400 ml) and H_2O (200 ml), dried ($MgSO_4$), and evaporated. The residue was further dried under high vacuum for 24 h to give crude **9** (41.18 g, 123%), as a brown honey which was purified by FC (hexane/AcOEt 3:1 $\rightarrow$1:1.25): **9** (21.36 g, 64%) as slighly yellow, microcrystalline solid. An anal. sample was obtained by prep. HPLC (hexane/AcOEt 2:1, flow: 16 ml/min, detection at 254 nm, t_R 16.6 min). M.p. 61°. R_f (hexane/AcOEt 1:1) 0.51. R_f (toluene/AcOEt 3:1) 0.27. $[\alpha]_D^{21} = +5.1$ ($c = 1.144$, $CHCl_3$). IR ($CHCl_3$): 3510/3395*w-m*, 3060/3020/3000*w*, 2960/2920/2860*w*, 1730*w*, 1685v*s*, 1565/1495/1452*m*, 1390/1370/1330/1310/1250*w-m*, 1190*m*(sh), 1150–1080*s*(br.), 1068v*s*, 1028*s*, 698*s*. ^{1}H-NMR (400 MHz, C_6D_6): 3.69 (*dd*, $^2J(5,5') = 10.7$, $^3J(5,4) = 4.4$, H–C(5)); 3.78 (*dd*, $^2J(5',5) = 10.7$, $^3J(5',4) = 2.1$, H′–C(5)); 4.00 (*ddd*, $^3J(4,3) = 8.4$, $^3J(4,5) = 4.5$, $^3J(4,5') = 2.15$, H–C(4)); 4.16 (*d*, $^2J_{gem} = 11.5$, 1 H, PhCH_2); 4.27–4.32 (*m*, 4 H, PhCH_2); 4.43 (*d*, $^3J(2,3) = 2.4$, H–C(2)); 4.50 (*dd*, $^3J(3,2) = 2.4$, $^3J(3,4) = 8.4$, H–C(3)); 4.62 (*d*, $^2J_{gem} = 11.1$, 1 H, PhCH_2); 4.66 (*d*, $^2J_{gem} =$ 11.9, 1 H, PhCH_2); 4.83 (*d*, $^2J_{gem} = 11.1$, 1 H, PhCH_2); 6.39 (br. *d*, $^2J_{gem} = 3.57$; with D_2O $\rightarrow$ br. *s* at 6.40 (*ca.* 30% exchange, 1 H, CONH_2); 6.72 (br. *d*, $^2J_{gem} = 3.52$; with $D_2O \rightarrow$ br. *s* at 6.71 (*ca.* 30% exchanged, 1 H, CONH_2); 7.03–7.16 (*m*, 14 arom. H); 7.24–7.32 (*m*, 6, arom. H). ^{13}C-NMR (100 MHz, C_6D_6): 69.31 (*t*, C(5)); 71.93, 73.37, 73.72, 75.13 (4*t*, PhCH_2); 78.27 (*d*, C(4)); 79.87 (*d*, C(3)); 80.69 (*d*, C(2)); 127.54, 127.61, 127.66, 127.70, 127.87, 127.95, 127.98, 128.35, 128.47, 128.52, 128.57, 128.64 (12*d*, arom. C); 138.11, 138.99, 139.08, 139.34 (4*s*, C_{ipso}(Ph)); 174.84 (*s*, C(1)). CI-MS (NH_3): 528(7), 527(37, $[M+2]^+$), 526(100, $[M+1]^+$), 166(8), 148(19). Anal. calc. for $C_{33}H_{35}NO_5$ (525.65): C 75.41, H 6.71, N 2.66; found: C 75.53, H 6.90, N 2.65.

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[7]) The concentration of the BuLi solns. did not have to be determined beforehand, since deprotonation of **9** was very conveniently followed: the colour of the soln. changed from yellow to orange after addition of exactly 1.0 equiv. of BuLi, as during the titration of BuLi with 1,3-diphenylacetone tosylhydrazone [49].

2,3,4,5-Tetra-O-*benzyl*-N-*[2-(benzyloxy)-2-oxoethyl]*-D-*arabinonamide* (= *Benzyl* N-*(2,3,4-Tetra*-O-*benzyl*-D-*arabinonoyl)glycinate*; **12**). A soln. of **9** (520 mg, 0.989 mmol) in abs. THF/DMPU 14:8 (22 ml) at −85° was titrated with BuLi (*Fluka*, *ca.* 1.35M, in hexane, *ca.* 1.0 ml), until the colour of the soln. changed from yellow to orange[7]). A soln. of *benzyl [(trifluoromethyl)sulfonyloxy]acetate* (**10**; 415 mg, 1.391 mmol) in abs. THF (2 ml) was added after 5 min in one portion. Stirring was continued until the soln. had reached −25° (*ca.* 3.5 h). After 60 h at −25°, the mixture was poured on sat. aq. NH_4Cl soln. (25 ml) and diluted with Et_2O (25 ml). The org. phase was separated and the aq. phase extracted with Et_2O (4 × 30 ml). The combined org. phases were washed with sat. aq. NaCl soln. (15 ml) and H_2O (15 ml), dried ($MgSO_4$), and evaporated, and the residue was purified by FC (toluene/AcOEt 10:1): **12** (302 mg, 45%). Slightly yellowish oil. R_f (toluene/AcOEt 5:1) 0.46. $[\alpha]_D^{21} = -10.4$ ($c = 1.140$, $CHCl_3$). IR ($CHCl_3$): 3405*m*, 3050/3020/2990/2970/2930/2895/2860*w*, 1742*s*, 1670*s*, 1520*m*, 1495*w-m*, 1450*m*, 1385/1355*w*, 1255/1235*w-m*, 1185*m-s*, 1100*s* (br.), 1065*s*, 1025*m*, 695*s*. ^{1}H-NMR (500 MHz, C_6D_6): 3.29 (*dd*, $^2J_{gem} = 18.0$, $^3J(NH) = 4.6$, 1 H, NCH_2COOBn); 3.71 (*dd*, $^2J(5,5') = 10.7$, $^3J(5,4) = 4.5$, H−C(5)); 3.81 (*dd*, $^2J(5',5) = 10.7$, $^3J(5',4) = 2.15$, H′−C(5)); 4.06–4.13 (*m*, $^3J(NH) = 7.1$, $^2J_{gem} = 18.0$, 2 H, H−C(4), NCH_2COOBn); 4.25 (*d*, $^2J_{gem} = 11.3$, 1 H, $PhCH_2$); 4.34 (*s*, 2 H, CH_2Ph); 4.38 (*d*, $^2J_{gem} = 11.9$, 1 H, CH_2Ph); 4.49–4.54 (*m*, $^3J(2,3) \approx 2.55$, $^3J(3,4) \approx 8.2$, 3 H, $PhCH_2$, H−C(2), H−C(3)); 4.63–4.89 (*m*, 5 H, $PhCH_2$); 6.94 (br. *dd*, $^3J(N,H) = 7.1$, 4.7; with D_2O no exchange, $CONHCH_2$); 7.02–7.16 (*m*, 18, arom. H); 7.26–7.34 (*m*, 7, arom. H). ^{13}C-NMR (125 MHz, C_6D_6): 40.74 (*t*, CH_2N); 66.81 (*t*, $PhCH_2$ (COOBn)); 69.43 (*t*, C(5)); 72.00, 73.39, 73.94, 75.11 (4*t*, $PhCH_2$ (OBn)); 78.31 (*d*, C(4)); 80.12 (*d*, C(3)); 80.94 (*d*, C(2)); 127.56, 127.61, 127.65, 127.67, 128.09, 128.30, 128.54, 128.55, 128.58, 128.65, 128.69, 128.71 (12*d*, arom. C); 136.03, 138.14, 139.04, 139.30, 139.36 (5*s*, C_{ipso}(Ph)); 169.53 (*s*, C(1)); 171.52 (*s*, *C*OOBn). CI-MS (NH_3): 676(18), 675(35, $[M+2]^+$), 674(100, $[M+1]^+$). Anal. calc. for $C_{42}H_{43}NO_7$ (673.81): C 74.87, H 6.43, N 2.08; found: C 74.77, H 6.40, N 1.97.

2,3,4,5-Tetra-O-*benzyl*-N-*[bis(benzyloxy)phosphinyl]methyl*-D-*arabinonamide* (= *Dibenzyl [(2,3,4,5-Tetra*-O-*benzyl*-D-*arabinonoyl)amino]methylphosphonate*; **13**). A soln. of **9** (588 mg, 1.186 mmol) in abs. THF/DMPU 2:1 (22.5 ml) at −78° was titrated with BuLi (*Fluka*, 1.4M, in hexane) until the colour of the soln. changed from yellow to orange (*ca.* 1.20 ml) and stirred at −78° for 10 min. A soln. of ([bis(benzyloxy)phosphinyl]methyl trifluoromethanesulfonate (**11**; 548 mg, 1.291 mmol) in abs. THF (2 ml) was injected through a septum. Stirring was continued until the cooling-bath temp. reached −25°. After 19 h at −25° (TLC: incomplete conversion), the soln. was cooled to −78°, and *t*-BuLi (0.26 ml, *Aldrich*, 1.33M in pentane) and additional **11** (160 mg, 0.377 mmol) were added. Stirring was continued until the cooling-bath temp. had reached −10°. Workup was the same as described for **12**. FC (toluene/AcOEt 3:1) of the crude product afforded **13** (811 mg, 90%) as a colourless, viscous oil. An anal. sample was obtained by prep. HPLC (hexane/AcOEt 1.7:1, flow: 16 ml/min, detection at 254 nm; t_R 34.6 min). R_f (toluene/AcOEt 1:1) 0.60. $[\alpha]_D^{21} = -10.5$ ($c = 0.917$, $CHCl_3$). IR ($CHCl_3$): 3405*m*, 3050/3020/2990/2940/2920/2890/2860*w*, 1675*s*, 1515*m-s*, 1495*w-m*, 1450*m*, 1390/1375/1360/1330/1305*w-m*, 1240*s*, 1140–1065*s* (br.), 1025/1005/995*s*, 695*s*. ^{1}H-NMR (500 MHz, C_6D_6): 3.15 (*ddd*, $^2J_{gem} = 15.7$, $^2J(H,P) = 10.2$, $^3J(N,H) = 4.6$; with P decoupling → *dd*, $^2J_{gem} = 15.8$, $^3J(N,H) = 4.6$, 1 H, $NCH_2PO_3Bn_2$); 3.68 (*dd*, $^2J(5,5') = 10.7$, $^3J(5,4) = 4.5$, H−C(5)); 3.78 (*dd*, $^2J(5',5) = 10.7$, $^3J(5',4) = 2.2$, H′−C(5)); 4.01 (*ddd*, $^3J(4,3) = 7.5$, $^3J(4,5) = 4.7$, $^3J(4,5') = 2.5$, H−C(4)); 4.09 (*ddd*, $^2J_{gem} = 15.75$, $^2J(H,P) = 13.0$, $^3J(N,H) = 8.0$, P decoupling → *dd*, $^2J_{gem} = 15.75$, $^3J(N,H) = 8.0$, 1 H, $NCH_2PO_3Bn_2$); 4.15 (*d*, $^2J_{gem} = 11.15$, 1 H, $PhCH_2$); 4.31 (*s*, 2 H, $PhCH_2$); 4.35 (*d*, $^2J_{gem} = 11.1$, 1 H, $PhCH_2$); 4.36 (*d*, $^2J_{gem} = 11.8$, 1 H, $PhCH_2$); 4.47–4.49 (*m*, H−C(2), H−C(3)); 4.59 (*d*, $^2J_{gem} = 11.4$, 1 H, $PhCH_2$); 4.69 (*d*, $^2J_{gem} = 11.8$, 1 H, $PhCH_2$); 4.73 (*d*, $^2J_{gem} = 11.4$, 1 H, $PhCH_2$); 4.82–4.92 (*m* (2 *AB*, strong signal overlap); P decoupling → 1 *AB*, 4 H, $P(OCH_2Ph)_2$); 6.96 (br. *t*, $^3J(N,H) \approx 5.5$, additional $^3J(H,P)$ not resolved, $CONHCH_2$); 6.98–7.29 (*m*, 30, arom. H). ^{13}C-NMR (125 MHz, C_6D_6): 35.04 (*dt*, $^1J(H,P) = 155.6$, CH_2N); 67.71, 67.76 (2*dt*, $^2J(C,P) = 2.0$, 2.1, $P(OCH_2Ph)_2$); 69.37 (*t*, C(5)); 69.37, 73.39, 73.97, 75.09 (4*t*, $PhCH_2$ (OBn)); 78.32 (*d*, C(4)); 80.08 (*d*, C(3)); 80.95 (*d*, C(2)); 127.57, 127.62, 127.63, 127.68, 128.08, 128.11, 128.45, 128.48, 128.50, 128.54, 128.58, 128.73, 128.75, (13*d*, arom. C); 136.81 (*d*, $^3J(C,P) = 5.9$, C_{ipso}(Ph)); 137.92, 139.01, 139.21, 139.37 (4*s*, C_{ipso}(OBn)); 171.17 (*d*, $^3J(C,P) = 4.3$, C(1)). ^{31}P-NMR (205.8 MHz, C_6D_6): 24.15 (*s*). CI-MS (NH_3): 801(13, $[M+2]^+$), 800(25, $[M+1]^+$), 386(9), 296(30), 295(11), 278(10), 277(7), 109(8), 108(100, $[BnOH]^+$). Anal. calc. for $C_{48}H_{50}NO_8P$ (799.90): C 72.07, H 6.30, N 1.75; found: C 71.90, H 6.20, N 1.87.

N-*(*D-*Arabinonoyl)glycine* (**2**). A soln. of **12** (358 mg, 0.531 mmol) in *t*-BuOH (7 ml) was added to $Pd(OH)_2$/C (20%, 206 mg) in the same solvent (5 ml) that had been stirred under H_2 at 10 bar for 30 min. The suspension was diluted with H_2O (3 ml), stirred vigourously under H_2 at 10 bar until UV-active compounds were no longer detected by TLC (*ca.* 110 h), diluted with H_2O (5 ml), treated with *Celite* (*ca.* 50 mg), and centrifuged. After collection of the supernatant, the sediment was thoroughly mixed with H_2O (10 ml) and centrifuged again. This procedure was repeated twice. The combined supernatants were lyophilized. The residue was taken up in H_2O

(*ca.* 2 ml), filled in a syringe, pressed through a membrane filter (0.2 μm, *Merck Anotop*) and again lyophilized. The free carboxylic acid **2** was obtained as colourless foam (108 mg, 91%). Prep. HPLC on a derivatized *RP*-phase (*NH*$_2$, 0.1M (Et_3NH)HCO_3 buffer, pH 7.1 adjusted with AcOH, 1% MeCN, refract. detection, flow 5 ml/min; t_R 26 min) yielded the triethylammonium salt **2**·Et_3N (152 mg, 86%). White powder. $[\alpha]_D^{21} = -25.9$ (c = 1.125, H_2O). IR (KBr): 3400*vs* (br.), 2970/2930/2870*m-w*, 2720/2675/2490*m*, 1742*s*, 1655*s*, 1600*s* (br.), 1540*m-s*, 1470*m*, 1430/1400*m-s*, 1330/1315/1285*w-m*, 1170*w*, 1130/1115/1090/1055/1025*s*, 910/885*w*. ^{1}H-NMR (500 MHz, D_2O): 1.24 (t, ^3J = 7.3, 9 H, *Me*CH_2N); 3.16 (q, ^3J = 7.3, 6 H, Me*C*H_2N); 3.64 (dd, ^2J(5,5′) = 11.8, ^3J(5,4) = 6.1, H–C(5)); 3.69–3.76 (m, $^2J_{gem}$ = 17.2, 2 H, H–C(4), N*C*H_2COO$^-$); 3.80–3.95 (m, $^2J_{gem}$ = 17.5, ^3J(3,4) = 8.9, ^3J(2,3) not resolved, ^3J(5′,4) = 2.5, 3 H, N*C*H_2COO$^-$, H′–C(5), H–C(3)); 4.42 (br. *s*, ^3J(2,3) < 1, H–C(2)). ^{13}C-NMR (125 MHz, D_2O): 10.95 (q, *Me*CH_2N); 45.73 (t, N*C*H_2COO$^-$); 49.36 (t, Me*C*H_2N); 65.70 (t, C(5)); 73.28 (d, C(4)); 73.64 (d, C(3)); 74.23 (d, C(2)); 177.88 (*s*, C(1)); 179.14 (*s*, COO$^-$). FAB-MS (neg. mode): 445 (32.5, [2*M* + H$^-$]), 223 (13.8, [*M* + H]$^-$), 222 (100, *M*$^-$), 183 (14, glycerol matrix), 132 (13.8), 91 (15.4, glycerol matrix). Anal. calc. for $C_{13}H_{28}N_2O_7 \cdot 2\ H_2O$ (360.40): C 43.32, H 8.94, N 7.77; found: C 43.65, H 8.34, N 7.98.

*(*D*-Arabinonoylamino)methylphosphonate* (**14**). To a suspension of Pd(OH)$_2$/C (20%, 390 mg) in *t*-BuOH/H_2O 4:1 (10 ml), **13** (615 mg, 0.7688 mmol) was added. The suspension was stirred vigourously under H_2 (9 bar), until TLC failed to detect UV-active products (*ca.* 70 h). Workup followed the procedure described for **2**. A soln. of the crude lyophilisate in H_2O (2 ml) was passed through a cation-exchange resin column (*Amberlyst 15*, Na^+ form, *ca.* 5 g). Product-containing fractions were collected and lyophilized. The residue was taken up in H_2O dest. (3 ml), filled in a syringe and pressed through a membrane filter (0.2 μm, *Merck Anotop*). The filtered soln. was lyophilized. The resulting sodium salt **14a** (191 mg, 82%) was purified by prep. HPLC on a quaternary ion exchange resin column (*SAX;* 0.1M (Et_3NH)HCO_3 buffer, pH 6.5 adjusted with AcOH, detection at 200 nm, flow 10 ml/min, t_R 13.2 min) to afford the triethylammonium salt **14b** (118 mg, 33%; purification not optimized) as colourless foam. Anal. HPLC (*SAX*, 0.1M (Et_3NH)HCO_3 buffer, pH 6.5 adjusted with AcOH, detection at 200 nm, flow: 2 ml/min): t_R 4.8 min. $[\alpha]_D^{21} = -23.1$ (c = 1.116, H_2O). IR (KBr): 3400*vs* (br.), 2970/2935/2850/2840*w*, 2680*m*, 2490*w-m*, 1645*s* (br.), 1540*m-s*, 1475/1435/1400*m*, 1360*w*, 1300*w* (br.), 1170/1140/1080/1035*s* (br.), 975/915*m* (br.). ^{1}H-NMR (400 MHz, D_2O): 1.27 (t, ^3J = 7.3, 13 H, *M*eCH_2N); 3.19 (q, ^3J = 7.3, 9 H, Me*C*H_2N); 3.34 (dd, $^2J_{gem}$ = 15.0, ^2J(H,P) = 10.4, 1 H, N*C*H_2PO_3); 3.46 (dd, $^2J_{gem}$ = 15.0, ^2J(H,P) = 12.9, 1 H, N*C*H_2PO_3); 3.67 (dd, ^2J(5,5′) = 11.7, ^3J(5,4) = 6.1, H–C(5)); 3.76 (ddd, ^3J(4,3) = 9.0, ^3J(4,5) = 6.1, ^3J(4,5′) = 2.8, H–C(4)); 3.85 (dd, ^2J(5′,5) = 11.7, ^3J(5′,4) = 2.7, H′–C(5)); 3.91 (dd, ^3J(3,2) = 1.6; ^3J(3,4) = 9.0, H–C(3)); 4.45 (br. t, ^3J(2,3) ≈ ^5J(H,P) ≈ 1.3, H–C(2)). ^{13}C-NMR (100 MHz, D_2O): 10.90 (q, *Me*CH_2N); 40.35 (dt, ^1J(C,P) = 142.2, N*C*H_2P); 49.34 (t, Me*C*H_2N); 65.67 (t, C(5)); 73.29 (d, C(4)); 73.64 (d, C(3)); 74.14 (d, C(2)); 177.60 (d, ^3J(C,P) = 6.05, C(1)). ^{31}P-NMR (121.5 MHz, D_2O): 14.99 (*s*). FAB-MS (neg. mode): 517 (27.2%, [2*M* + H$^-$]), 259 (15.0, [*M*H]$^-$), 258 (100, *M*$^-$), 242 (5.1, [phospholactone + H]$^-$), 241 (2.2, [phospholactone]$^-$), 240 (4.1), 183 (18.0, glycerol matrix), 167 (14.7), 110 (7.2), 91 (14.5, glycerol matrix). Anal. calc. for $C_{12}H_{29}N_2O_8P$ (mono(triethylammonium) salt)/$C_{18}H_{44}N_3O_8P$ (bis(triethylammonium) salt) 1:1 · 1.5 H_2O (437.96): C 41.14, H 9.09, N 8.00; gef.: C 41.64, H 8.72, N 7.53.

2,3,4,5-Tetra-O-*benzyl*-N-*(2-bromoethyl)*-D-*arabinonamide* (**16**). A soln. of **9** (1400 mg, 2.663 mmol) in dry THF/DMPU 2:1 (30 ml) at −78° was titrated with *t*-BuLi (*Aldrich*, in pentane, *ca.* 1.25M) under vigourous stirring until the colour of the soln. changed from yellow to orange (*ca.* 1.8 ml) and stirred for 10 min at −78°. A precooled (−20°) soln. of *2-bromoethyl trifluoromethanesulfonate* (**15**)[8]) (2118 mg, 8.24 mmol) in dry THF (2.2 ml) was added dropwise. After the addition was complete, the colour of the soln. changed from orange to lemon-yellow. Stirring was continued until the cooling-bath temp. had reached −25°. The mixture was poured into sat. aq. NH_4Cl/sat. aq. NaCl soln. 1:1 (50 ml). The pH was adjusted to 7.0 with 1M phosphate buffer. Extraction with Et_2O (5 × 50 ml) was followed by washing of the combined org. phases with sat. aq. NaCl soln. (2 × 20 ml) and H_2O (10 ml). Drying (Na_2SO_4) and evaporation under reduced pressure gave a yellow oil which was further dried under high vacuum (20 h) and purified by FC (toluene/AcOEt 3:1): **16** (710 mg, 42%) as slightly yellowish oil, besides starting material **9** (600 mg, 43%). An anal. sample was obtained by prep. HPLC (hexane/AcOEt 4:1, flow: 16 ml/min, detection at 254 nm, t_R: 20.6 min). Colorless oil. R_f (hexane/AcOEt 3:1) 0.28. R_f (toluene/AcOEt 1:1) 0.79. $[\alpha]_D^{21} = -13.2$ (c = 0.535, $CHCl_3$) −13.2°. IR ($CHCl_3$): 3405*m*, 3070/3050/2990/2920/2860*w*, 1670*s*, 1515*m-s*, 1492/1450/1435*w-m*, 1360/1330*w*, 1300*w-m*, 1240*m*, 1190/1090/1065*s*, 1025/1010*m* (sh), 695*s*. ^{1}H-NMR (500 MHz, C_6D_6): 2.67–2.70 (m, 1 H, C*H*$_2$N); 2.87–2.94 (m, C*H*$_2$Br); 3.41–3.48 (m, 1 H, C*H*$_2$N); 3.70 (dd, ^2J(5,5′) = 10.7, ^3J(5,4) = 4.45, H–C(5)); 3.81 (dd, ^2J(5′,5) = 10.7, ^3J(5′,4) =

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[8]) Prepared according to the procedure of *Welsh* and co-workers [30]: yield 61%; colourless liquid, purified by distillation *in vacuo*. B.p. 33–35°/0.25 Torr ([30]: 50°/0.5 Torr).

2.15, H′–C(5)); 4.05 (*ddd*, ^3J(4,3) = 8.3, ^3J(4,5) = 4.4, ^3J(4,5′) = 2.2, H–C(4)); 4.24 (*d*, $^2J_{gem}$ = 11.35, 1 H, PhCH_2); 4.31–4.33 (*m*, 3 H, PhCH_2); 4.37 (*d*, $^2J_{gem}$ = 11.8, 1 H, PhCH_2); 4.46 (*d*, ^3J(2,3) = 2.5, H–C(2)); 4.50 (*dd*, ^3J(3,2) = 2.5, ^3J(3,4) = 8.3, H–C(3)); 4.62–4.69 (*m* (*AB*), 2 H, PhCH_2); 4.72 (*d*, $^2J_{gem}$ = 11.8, 1 H, PhCH_2); 6.77 (br. *t*, ^3J(H,N) ≈ 5.7, CONH); 7.05–7.17 (*m*, 12, arom. H); 7.25–7.31 (*m*, 8, arom. H). ^{13}C-NMR (125 MHz, C_6D_6): 31.91 (*t*, CH_2Br); 40.72 (*t*, CH_2N); 69.32 (*t*, C(5)); 71.94, 73.42, 74.18, 75.06 (4*t*, PhCH_2); 78.30 (*d*, C(4)); 80.10 (*d*, C(3)); 81.06 (*d*, C(2)); 127.62, 127.64, 127.67, 127.72, 127.88, 128.19, 128.50, 128.57, 128.60, 128.76 (10*d*, arom. C); 138.01, 138.98, 139.20, 139.32 (4*s*, C_{ipso}(Ph)); 171.15 (*s*, C(1)). CI-MS (NH_3): 634 (0.83, $[M+2]^+$), 632 (0.75, M^+) (M^+(^{79}Br)/$[M+2]^+$(^{81}Br) *ca.* 1:1 → 1 Br), 554 (8, $[M+2-HBr]^+$), 553 (40, $[M+1-HBr]^+$), 552 (100, $[M-H^{79}Br]^+$ or $[M+2-H^{81}Br]^+$). Anal. calc. for $C_{35}H_{38}BrNO_5$ (632.59): C 66.45, H 6.05, Br 12.63, N 2.21; found: C 66.51, H 6.02, Br 12.33, N 2.39.

N-*(2,3,4,5-Tetra*-O-*benzyl*-D-*arabinonoyl)taurine* (= *Sodium 2-[(2,3,4,5-Tetra*-O-*benzyl*-D-*arabinonoyl)-amino]ethanesulfonate*; **17**) *and* N-*(*D-*Arabinonoyl)taurine Salt* (= *Sodium* or *Triethylammonium (*D-*Arobinonylamino)ethanesulfonate*; **18**). To a soln. of **16** (555 mg, 0.877 mmol) in EtOH (99%, 10 ml) was added Na_2SO_3 (111 mg, 0.877 mmol) and H_2O (3.6 ml). The white suspension was boiled under reflux at 80° under Ar for 17 h, cooled to r.t., diluted with MeOH (20 ml), and evaporated. The residue was purified by FC (CH_2Cl_2/MeOH 20:1) to give **17**[9]) (290 mg, 50%) as slightly yellow oil, which was dissolved in *t*-BuOH (7 ml) and added to a suspension of Pd(OH)$_2$/C (20%, 300 mg) in *t*-BuOH (5 ml) that had been stirred under 10 bar H_2 for 30 min. After dilution with H_2O (3.0 ml), the suspension was stirred vigourously at r.t. under H_2 (10 bar) for 17 h. Workup as described for **2** afforded the sodium salt **18a** (113 mg, 88%) as colourless solid. Further purification by prep. HPLC (*NH*$_2$, isocratic 0.1M (Et_3NH)HCO_3 buffer, pH 6.8–7.0 adjusted with AcOH; 1% MeCN; detection at 200 nm, flow: 5 ml/min, t_R 19.5 min) afforded the triethylammonium salt **18b** (128 mg, 78%) as colourless, amorphous solid.

Data of **17**: R_f (CH_2Cl_2/MeOH 20:1) 0.23. ^{13}C-NMR (75 MHz, CD_3OD): 42.64 (*t*, CH_2N); 61.40 (*t*, CH_2SO_3Na); 69.11 (*t*, C(5)); 78.86 (*d*, C(4)); 80.62 (*d*, C(3)); 80.95 (*d*, C(2)); 128.78, 129.19, 129.35, 129.46, 129.57 (5*d*, arom. C); 130.92, 138.62, 139.48, 139.93 (4*s*, C_{ipso}(Ph)); 174.19 (*s*, C(1)).

Data of **18b**: Anal. *HPLC* (*NH*$_2$, 0.1M (Et_3NH)HCO_3 buffer; pH 7.2 adjusted with AcOH; 2% MeCN; refract. detection, flow, 0.5 ml/min): t_R 5.9 min. $[\alpha]_D^{21}$ = −29.6 (*c* = 0.706, H_2O). IR (KBr): 3480/3380v*s*(br.), 2970/2930/2880*w*, 2680/2570/2500/2420*m*-*s*, 1645v*s*, 1560*s*, 1445/1425*m*, 1370/1330*w*, 1290/1260/1230/1205*m*, 1110/1090/1080/1055/1040*s*. ^{1}H-NMR (500 MHz, D_2O): 1.24 (*t*, ^3J = 7.3, 9 H, *Me*CH_2N); 3.16 (*q*, ^3J = 7.35, 6 H, MeCH_2N); 3.34–3.43 (*m* (*AA′*), CH_2SO_3); 3.62–3.66 (*m*, CONHCH_2, H–C(5)); 3.72 (not fully resolved *ddd*, ^3J(4,5) = 6.2, ^3J(4,5′) = 2.8, H–C(4)); 3.82 (*dd*, ^2J(5′,5) = 11.8, ^3J(5′,4) = 2.8, H′–C(5)); 3.86 (*dd*, ^3J(3,2) = 1.6; ^3J(3,4) = 9.1, H–C(3)); 4.40 (*d*, ^3J(2,3) = 1.6, H–C(2)). ^{13}C-NMR (125 MHz, D_2O): 10.96 (*q*, *Me*CH_2N); 43.89 (*t*, CONCH_2); 49.37 (*t*, MeCH_2N); 62.73 (*t*, CH_2SO_3); 65.68 (*t*, C(5)); 73.33 (*d*, C(4)); 73.59 (*d*, C(3)); 74.18 (*d*, C(2)); 178.32 (*s*, C(1)). FAB-MS (neg. mode): 417 (9.9, $[2(M-SO_2)+H]^+$), 304 (12.9), 209 (10.5), 208 (100, $[M-SO_2]^-$), 206 (9.7), 183 (26.8, glycerol matrix), 168 (12.3), 165 (35.7), 153 (11.8), 118 (11.4), 91 (17.5, glycerol matrix). Anal. calc. for $C_{13}H_{30}N_2O_8S \cdot 0.5\ H_2O$ (383.46): C 40.72, H 8.15, N 7.31; found: C 40.72, H 8.12, N 7.48.

2,3,4,5-Tetra-O-*benzyl*-N-*[2,2-bis(diethoxyphosphinyl)ethyl]*-D-*arabinonamide* (= *Tetraethyl {2-[(2,3,4,5-Tetra*-O-*benzyl*-D-*arabinonoyl)amino]ethylidene}bis[phosphonate]*; **20**). A soln. of *t*-BuOK in *t*-BuOH (*Aldrich*, 1.0M, 0.47 ml, *ca.* 0.47 mmol) was added at 40° to a soln. of **9** (1232 mg, 2.343 mmol) in dry *t*-BuOH (25 ml) under Ar. Stirring was continued for 5 min. A soln. of *tetraethyl ethenylidenebis[phosphonate]* (**19**)[10]) (774 mg, 2.578 mmol) in *t*-BuOH (2.5 ml) was injected through a septum. After stirring at 40° for 43 h, the temp. was increased to 50°, and additional **19** (70 mg, 0.2343 mmol, 0.1 equiv.) was added. After 67 h, the same amount of **19** and more *t*-BuOK soln. (0.235 ml, 0.234 mmol, 0.1 equiv.) were added. After a total reaction time of 92 h, the soln. was cooled to r.t. and poured onto a mixture of sat. aq. NH_4Cl soln. (25 ml), sat. aq. NaCl soln. (15 ml), and Et_2O (25 ml). The org. phase was separated. The aq. phase was diluted with sat. aq. NaCl soln. (25 ml), and extracted with Et_2O (4 × 25 ml). The combined org. phases were washed with sat. aq. NaCl soln. (10 ml), dried ($MgSO_4$), and evaporated. The resulting amber oil was purified by FC (toluene/acetone 1:1): **20**

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[9]) The intermediate tetra-*O*-benzyl-protected sodium sulfonate **17** is readily soluble in common org. solvents (THF, Et_2O, AcOEt, CH_2Cl_2) and was conveniently purified by FC.

[10]) Synthesized from tetraethyl ethylenebis[phosphonate] according to the procedure of *Charlton* and *Alauddin* [50], and *Degenhardt* and *Burdsall* [36] [38], and purified by fractional distillation *in vacuo:* B.p. 120–125°/0.4 Torr; R_f (toluene/acetone 1:1) 0.22. ^{13}C-NMR (C_6D_6): 147.9 (*t*, CH_2 =). ^{31}P-NMR (C_6D_6): 13.3 (*s*).

(1.753 g, 90%) as slightly yellow oil. An anal. sample was obtained by prep HPLC ($CHCl_3$/Et_2O 10:1). Colourless oil. R_f (toluene/acetone 1:1) 0.35. $[\alpha]_D^{21} = -11.9°$ ($c = 0.852$, $CHCl_3$). IR ($CHCl_3$): 3400*m*, 3060/2985/2920/2890/2850*w*, 1665*s*, 1515*m-s*, 1495*w-m*, 1450*m*, 1390/1375/1350*w-m*, 1250*s*, 1090/1060/1020/970*s*, 695*s*. ^{1}H-NMR (500 MHz, C_6D_6): 1.00–1.09 (*m*, 12 H, *Me*CH_2OP); 2.61 (*tt*, ^3J(CH,CH_2) = 5.9, ^2J(CH,P) = ^2J(CH,P′) = 23.1 P decoupling → *t*, ^3J(CH,CH_2) = 5.9, C*H*(PO_3Et_2)$_2$); 3.71 (*dd*, ^2J(5,5′) = 10.7, ^3J(5,4) = 4.6, H–C(5)); 3.80 (*dd*, ^2J(5′,5) = 10.7, ^3J(5′,4) = 2.1, H′–C(5)); 3.92–4.12 (*m*, P decoupling → strongly changed *m*, 10 H, H–C(4), CH_2N, MeC*H*$_2$OP); 4.29–4.32 (*m*, 3 H, PhC*H*$_2$, C*H*$_2$N); 4.39 (*d*, $^2J_{gem}$ = 12.1, 1 H, PhC*H*$_2$); 4.57 (*d*, ^3J(2,3) = 2.5, H–C(2)); 4.60 (*dd*, ^3J(3,2) = 2.5, ^3J(3,4) = 8.2, H–C(3)); 4.66 (*d*, $^2J_{gem}$ = 11.4, 1 H, PhC*H*$_2$); 4.71 (*d*, $^2J_{gem}$ = 11.9, 1 H, PhC*H*$_2$); 4.79 (*d*, $^2J_{gem}$ = 11.0, 1 H, PhC*H*$_2$); 4.81 (*d*, $^2J_{gem}$ = 11.3, 1 H, PhC*H*$_2$); 7.05–7.49 (*m*, 20, arom. H); 8.09 (br. *t*, ^3J(NH,CH_2) ≈ 5.8, additional ^4J to P-atoms not resolved, P decoupling → sharp *dd*, ^3J(NH,CH_2) = 5.1, 6.7, NHCO). ^{13}C-NMR (125 MHz, C_6D_6): 16.34, 16.36, 16.39, 16.42 (4*q*, *Me*CH_2OP); 38.67 (*td*, ^1J(CH,P) = ^1J(CH,P′) = 131.3, CH_2C*H*(PO_3Et_2)$_2$); 39.90 (*tt*, ^2J(CH_2,P) = 4.6, CH_2N); 62.64 (*dt*, ^2J(CH_2,P) = 6.4, MeC*H*$_2$OP); 62.80 (*dt*, ^2J(CH_2,P) = 7.4, MeC*H*$_2$OP); 62.85 (*dt*, ^2J(CH_2,P) = 6.7, MeC*H*$_2$OP); 62.98 (*dt*, ^2J(CH_2,P) = 6.3, MeC*H*$_2$OP); 69.57 (*t*, C(5)); 71.97, 73.36, 74.36, 75.04 (4*t*, PhC*H*$_2$); 78.50 (*d*, C(4)); 80.27 (*d*, C(3)); 81.20 (*d*, C(2)); 127.49, 127.51, 127.57, 127.61, 127.92, 128.46, 128.53, 128.55, 128.71 (9*d*, arom. C); 138.43, 139.12, 139.39, 139.52 (4*s*, C_{ipso}(Bn)); 171.08 (*s*, C(1)). ^{31}P-NMR (205.8 MHz, C_6D_6): 21.72 (*d*, ^2J(P,P′) = 1.65); 21.81 (*d*, ^2J(P′,P) = 1.44). CI-MS (NH_3): 828(13), 827 (49, $[M+2]^+$), 826 (100, $[M+1]^+$), 526 (20, $[M+1-CH_2CH(PO_3Et_2)]^+$), 301 (13, $[CH_2CH(PO_3Et_2)]^+$). Anal. calc. for $C_{43}H_{57}NO_{11}P_2$ (825.87): C 62.54, H 6.96, N 1.69, P 7.50; found: C 62.28, H 6.70, N 1.72, P 7.21.

N-*(2,2-Diphosphonoethyl)*-D-*arabinonamide* (= *[2-(*D*-Arabinonoylamino)ethylidene]bis[phosphonic acid]*; **22a**). A soln. of **20** (2.259 g, 2.73 mmol) in *t*-BuOH (25 ml) was added to a suspension of $Pd(OH)_2$/C (20%, 980 mg) in *t*-BuOH (15 ml) and prehydrogenated under 10 bar H_2 for 30 min. After dilution with H_2O (10 ml), the suspension was stirred vigourously under 10 bar H_2 for 6 d. *Celite* (100 mg) was added, and the Pd catalyst was removed by centrifugation. The supernatant was removed and the residue suspended in MeOH (60 ml) and again centrifuged. This procedure was repeated twice. The combined supernatants were concentrated to a small volume and pressure-filtered over a 0.2-μm membrane filter (*Merck*, *Anotop*). The filtrate was evaporated. The residue was dissolved in 50 ml of H_2O and lyophilized. The resulting yellow gum of **21** was dried under high vacuum (96 h) over P_4O_{10} and dissolved in dry CH_2Cl_2 (60 ml) under Ar, and the soln. was stirred at −15° for 15 min. Me_3SiBr (8.83 ml, 68.25 mmol, 25 equiv.) was added dropwise through a septum within 15 min. The cooling bath was removed after 1 h. After stirring at r.t. for 48 h, the yellow soln. was evaporated and kept under high vacuum for 2 h, before the solid foamy residue was taken up in H_2O/MeOH 1:6 (50 ml) and shaken vigourously. After a few min, the white suspension turned into a clear yellow soln., which was suction-filtered through a sand/*Celite*/sand bed, concentrated to a small volume, and lyophilized. The residue was taken up in H_2O (60 ml), pressure-filtered through a 0.2-μm membrane filter (*Merck*, *Anotop*) and lyophilized again to afford the free acid **22a** (1.786 g, 88%) as colourless foam. An anal. sample was obtained by prep. HPLC (*CN*, 0.1M $(Et_3NH)HCO_3$ buffer, 1% MeCN, pH 7.15 adjusted with AcOH, flow: 5 ml/min, refract. detection t_R 13.2 min): 210 mg of **22a** yielded 98 mg of the tetrakis(triethylammonium) salt **22b** as colourless fluffy solid (purification not optimized). M.p. 135–140° (dec.). $[\alpha]_D^{21} = +6.6$ ($c = 0.738$, H_2O). IR (KBr): 3400*s* (br.), 2970/2930*w-m*, 2740/2675*w*, 1780*m*, 1630*m*, 1495/1435/1395*m*, 1170*s* (br.), 1035*s*. ^{1}H-NMR (500 MHz, D_2O): 1.25 (*t*, $^3J_{vic}$ = 7.3, 36 H, *Me*CH_2N); 2.24 (br. *t*, ^2J(CH,P) = ^2J(CH,P′) = 20.9, additional coupling to CH,N *ca.* 6; P decoupling → br. *d*, 1 H, CH_2C*H*(PO_3H_2)$_2$); 3.17 (*q*, $^3J_{vic}$ = 7.3, 24 H, MeC*H*$_2$N); 3.39 (*td*, $^3J_{vic}$ = 6.3; ^3J(CH_2,P) = ^3J(CH_2,P′) = 14.9; P decoupling → br. *d*, CH_2N); 3.63 (*dd*, ^2J(5,5′) = 11.7, ^3J(5,4) = 6.4, H–C(5)); 3.70 (*m*, H–C(4)); 3.81 (*dd*, ^3J(3,2) = ^3J(3,4) = 8.9, H–C(3)); 3.82 (*dd*, ^2J(5′,5) = 11.7, ^3J(5′,4) = 2.6, H′–C(5)); 4.20 (*d*, ^3J(2,3) = 1.7, H–C(2)). ^{13}C-NMR (125 MHz, D_2O): 10.94 (*q*, MeC*H*$_2$N); 39.73 (*td*, ^1J(CH,P) = ^1J(CH,P′) = 115.1, CH_2C*H*(PO_3H_2)$_2$); 40.16 (*t*, CONHC*H*$_2$); 49.38 (*t*, MeC*H*$_2$N); 65.82 (*t*, C(5)); 73.92 (*d*, C(4)); 74.24 (*d*, C(3)); 74.91 (*d*, C(2)); 183.69 (*s*, C(1)). FAB-MS (neg. mode, amide bond is cleaved under FAB conditions, *i.e.*, only A^-, the corresponding (2-aminoethylidene)bis[phosphonate] is observable): 818 (1.3, $[A_4H_3]^-$), 613 (3.3, $[A_3H_2]^-$), 408 (33.0, $[A_2H]^-$), 388(6.5), 296(16.7), 275 (6.5, glycerol matrix), 232(10), 204 (100, A^-), 186(12.1), 183 (43.9, glycerol matrix), 153(5.4), 91 (25.4, glycerol matrix).

3. *Thiobarbituric Acid Assay* [43–45]. According to the procedure of *Schauer* ('*Micro-Warren*') [51] in phosphate buffer of pH 5.9 with a 15 min inhibitor preincubation period. *S. typhimurium*, *Influenza A* (N9), and *Influenza B* (B/Lee/40) sialidase, and the fetuin (from fetal calf serum) used as enzyme substrate were kindly provided by Prof. *Laver* (Influenza Research Unit, Australian National University, Canberra, Australia). *Vibrio cholerae* sialidase was obtained in protease-free quality from *Boehringer Mannheim*. Enzyme dilutions with suitable activity for the assay conditions were found from preliminary experiments without inhibitor. Values in the *Table* reflect the relative enzyme activities as estimated from visual inspection of the relative colour intensity

of the pink β-formylpyruvate/thiobarbituric-acid complex formed in the enzymatic reaction in inhibitor experiments (15 min preincubation) as compared to reference experiments without inhibitors (= 100%). For better comparison, a reference inhibitor (DANA) was always tested in the same assay. In addition to blank experiments to account for nonenzymatic hydrolysis, separate inhibitor blanks were run in parallel to check for inhibitor-mediated substrate hydrolysis, which was not observed for any of the inhibitors tested. The activities observed are the result of duplicate experiments.

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