Sialyltransferase Inhibitors Based on CMP-Quinic Acid

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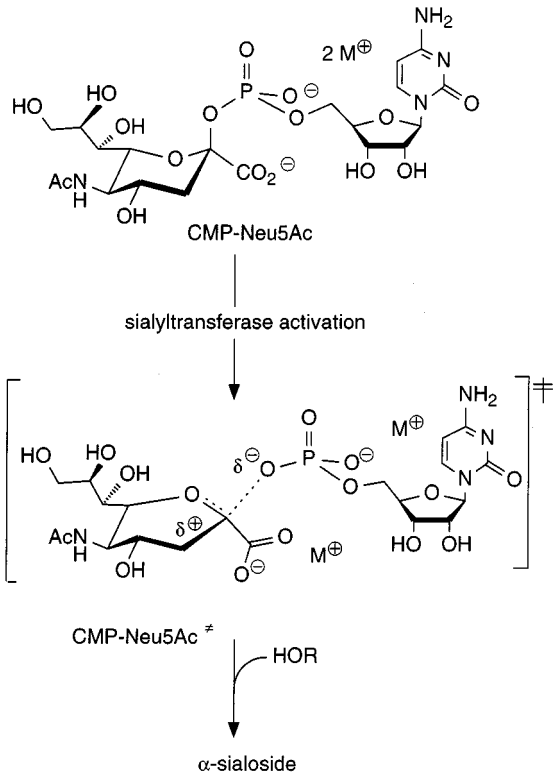
Quinic acid was transformed into phosphitamides **16**, **25**, and **36**, which could be readily linked to 5′-*O*-unprotected cytidine derivative **17**. Ensuing oxidation of the obtained phosphite triesters with tBuO$_2$H and hydrogenolytic de-*O*-benzylation furnished the corresponding phosphate diesters **18**, **26**, and **38**. Base catalyzed removal of acetyl protecting groups, and methyl ester hydrolysis furnished CMP-Neu5Ac analogues **1d**, **1e**, and **2**. Quinic acid was also transformed into 1,2-unsaturated diallyl α-hydroxymethyl-phosphate derivatives (*R*)- and (*S*)-**46**, which on reaction with cytidine phosphitamide **47** afforded the phosphite triesters. Subsequent oxidation with tBuO$_2$H and then treatment with NEt$_3$ gave phosphate diester derivatives (*R*)- and (*S*)-**48**. Deallylation, acetyl group removal, and methyl ester hydrolysis furnished (*R*)- and (*S*)-**3**, respectively. Treatment of (*R*)- and (*S*)-**48** with DBU as a base led to acetic acid elimination, thus yielding, after de-*O*-allylation, acetyl group cleavage, and ester hydrolysis, diene derivative (*E*)-**4**. Donor substrate analogues **1d** and **1e** exhibited good α(2–6)-sialyltransferase inhibition (K_i: $2.0\cdot10^{-4}$ and $2.0\cdot10^{-5}$ M). However, transition state analogues (*R*)-, and particularly (*S*)-**3** showed excellent inhibition properties (K_i: $1.6\cdot10^{-6}$ and $2.7\cdot10^{-7}$ M).

Introduction

Sialic acid containing glycoconjugate epitopes are involved in various biological interactions, such as the many forms of cell adhesion, thus influencing a variety of physiologically and pathologically important processes.[1] Recently, an interesting correlation between α(2–6)-sialylation of *N*-acetyllactosamine and B lymphocyte activation an immune function was reported, which could find medicinal application.[2] Therefore, in order to study the influence of sialyl residues in biological systems, it is highly desirable to develop efficient inhibitors for sialyltransferases.

The various sialyltransferases employ, independent of their source and their acceptor specificity, cytidine monophosphate *N*-acetylneuraminic acid (CMP-Neu5Ac, Scheme 1) as the donor substrate. As was recently shown by us,[3–6] structural analogues of the donor and particularly of the transition state CMP-Neu5Ac$^{\neq}$ of the donor (Scheme 1) exhibit high affinity to sialyltransferases; therefore, they are valuable inhibitors.[3–7] We present here new sialyltransferase inhibitors, which are based on quinic acid transformations; also their inhibition properties towards α(2–6)-sialyltransferase from rat liver (EC 2.4.99.1) will be communicated.[8]

An efficient inhibitor requires high binding affinity to the active site (generally provided by substrate and/or transition state analogues with competitive binding) and high stability under physiological conditions. Following previous reports, binding of donor analogues to sialyltransferases requires the CMP moiety or at least a nucleoside monophosphate residue,[9] yet structural variations in the phosphate group and the 4-, 5-, or 9-position of the Neu5Ac residue[10–12] are tolerated. Additionally, in order to block the transferase



Scheme 1. Mechanism of the sialylation

potential of the enzymes, stability of the glycosidic bond is required. All these demands can be almost ideally fulfilled by quinic acid and derivatives having the CMP moiety attached to the tertiary hydroxy group. Therefore, we initiated a programme for the synthesis of this type of compound[8,13] – typical examples are compounds of type **1–4** (Scheme 2). The synthesis of compounds **1a–c** has been previously reported.[3] Compounds **1d** and **1e** are donor

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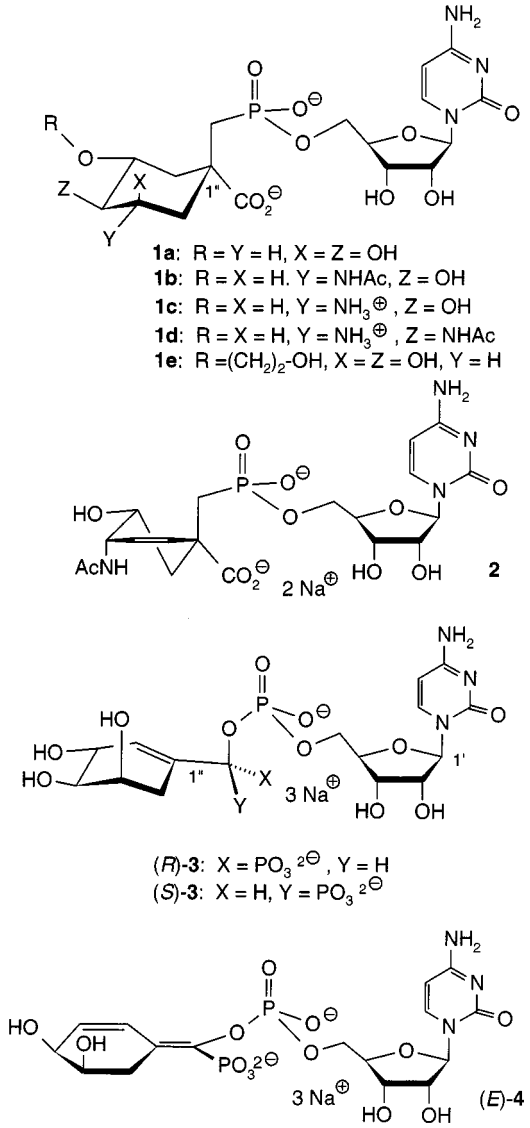


Scheme 2. Target molecules

substrate analogues having an amino group in 3′′-position or, alternatively, a side chain mimic in 5′′-position. Compounds **2**, and particularly **3** and **4**, are – as recently discussed[5,6] – transition state analogues of CMP-Neu5Ac.

Results and Discussion

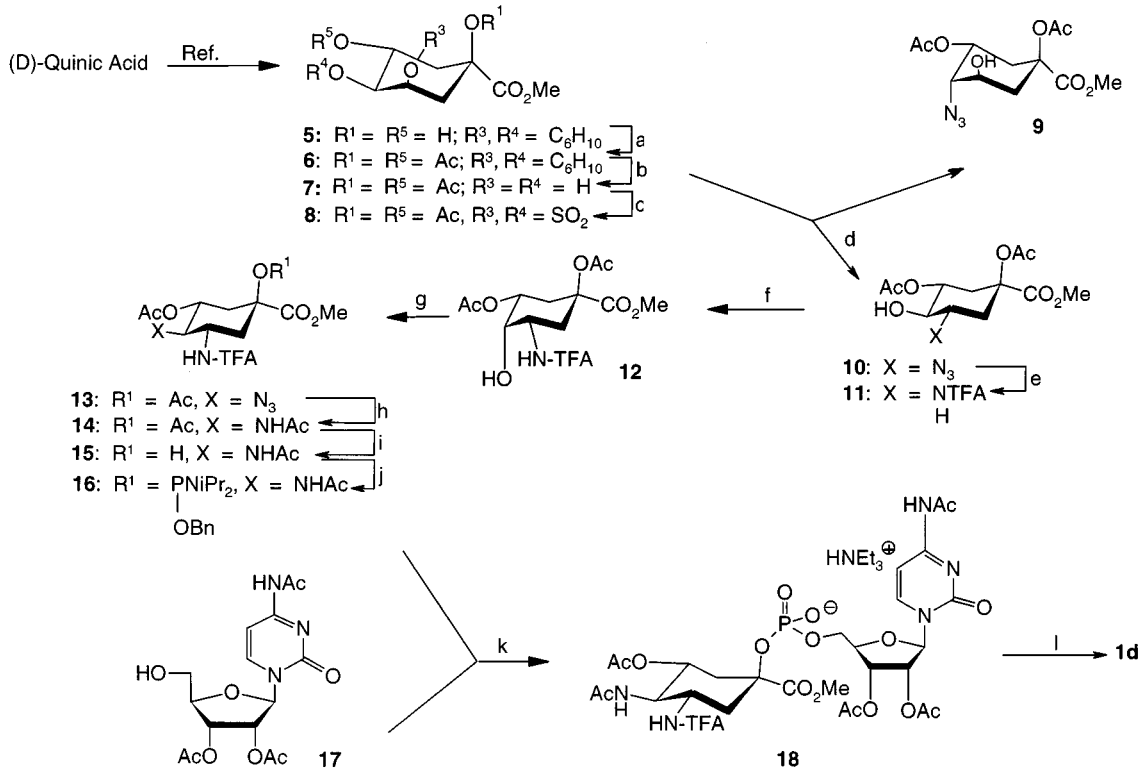
Synthesis of Donor Analogues 1d and 1e

For the synthesis of CMP-quinic acid derivative **1d**, quinic acid was transformed into known 3,4-*O*-cyclohexylidene derivative **5**[14] (Scheme 3). Ensuing *O*-acetylation with acetic anhydride in pyridine (→ **6**), then de-*O*-cyclohexylidenation with ethylmercaptan in the presence of *p*-toluenesulfonic acid (*p*TsOH) as catalyst[15] (→ **7**), and finally reaction with thionyl chloride in the presence of triethylamine as base and oxidation with $RuCl_3/NaIO_4$[16] afforded cyclic sulfate **8** in high overall yield. Nucleophilic substitution of **8** with lithium azide in DMF as solvent, and then hydrolysis of the attached sulfate group in aqueous sulfuric acid furnished a 2:5 mixture of **9** and desired azide **10**. Azide group reduction in **10** with hydrogen and Pd/C as the catalyst and then treatment with trifluoracetic anhydride $[(TFA)_2O]$ in the presence of $NaHCO_3$ gave trifluoroacetylamino derivative **11**.

For the introduction of the equatorial acetylamino group in 4-position, first inversion of configuration of the 4-hydroxy group in **11** was performed; to this end, the triflate was generated by treatment of **11** with trifluoromethanesulfonic anhydride (Tf_2O) in pyridine and then reaction with tetrabutylammonium nitrile[17] was carried out to afford the desired compound **12**. Activation of the 4-hydroxy group by triflate formation and then reaction with lithium azide in DMF at 60 °C led to azide **13**. Reduction of the azido group as described above and acetylation with acetic anhydride in pyridine furnished **14**, which possesses the equatorial 4-acetylamino group. De-*O*-acetylation of **14** under Zemplén conditions,[18] and then selective 5-*O*-acetylation with acetic anhydride in pyridine afforded **15**, which gave, on treatment with benzyloxy-chloro-diisopropylaminophosphane[19] in the presence of Hünig base, phosphitamide diester **16**.

The structural assignment of **13–16** can be derived from the ^{1}H-NMR data; for instance, **15**: $J_{3,4} = J_{4,5} = 10.6$ Hz. Condensation of **16** with known 5′-*O*-unprotected cytidine derivative **17**[3,8] in the presence of tetrazole as catalyst, then immediate oxidation of the phosphite triester with *tert*-butyl hydroperoxide and finally hydrogenolytic de-*O*-benzylation with Pd/C as catalyst afforded protected target molecule **18** in 32% overall yield from **16**. Deacetylation was carried out under Zemplén conditions,[18] which led to the formation of some lactam as by-product (by reaction of the ester moiety with the 3-amino group), thus supporting the structural assignments; for ester hydrolysis of the main product lithium hydroxide was employed. Preparative HPLC with triethylammonium bicarbonate as buffer and then ion exchange with Li^+ afforded pure **1d** as the dilithium salt in 67% yield.

Synthesis of CMP-quinic acid derivative **1e**, with a side chain mimic relating it more closely to CMP-Neu5Ac, started also from compound **5**. Selective 5-*O*-allylation was carried out with allyl trichloroacetimidate[20] in the presence of TfOH as catalyst, providing desired **19** in 90% yield (Scheme 4). 1-*O*-Acetylation of **19** to give **20** with acetic anhydride in pyridine required addition of Steglich base [4-(dimethylamino)pyridine, DMAP]. Ozonolysis of the allyl group in **20** and then treatment of the product with sodium borohydride afforded 5-hydroxyethyl derivative **21**. Reaction with acetic anhydride in pyridine furnished **22**, which on treatment with aqueous acetic acid led to de-*O*-cyclohexylidenated compound **23**. Cleavage of all *O*-acyl groups under Zemplén conditions[18] and then selective *O*-acetylation with acetic anhydride in pyridine gave 1-*O*-unprotected quinic acid derivative **24**. The same procedure as described for **16**, i.e. phosphitylation to give **25** and then reaction with **17** in the presence of tetrazole, subsequent oxidation with *tert*-butyl hydroperoxide, and hydrogenolytic debenzylation, gave protected target molecule **26** in 62% yield. Removal of



Scheme 3. Synthesis of **1d**. Reagents and conditions: (a) AcO, Pyr. – (b) EtSH, *p*TsOH, CH_2Cl_2. – (c) $SOCl_2$, NEt_3; $RuCl_3$, $NaIO_4$, MeCN/EtOAc/H_2O (68%). – (d) LiN_3, DMF; H_2SO_4, H_2O/THF (88%, **10/9** = 5:2). – (e) Pd/H_2; $(TFA)_2O$, $NaHCO_3$ (66%). – (f) Tf_2O, Pyr; $Bu_4N^+NO_2^-$ (55%). – (g) Tf_2O, Pyr; LiN_3, DMF (75%). – (h) Pd/C, H_2; Ac_2O, Pyr (72%). – (i) NaOMe, MeOH; Ac_2O, Pyr (81%). – (j) ClP(OBn)N*i*Pr_2EtN*i*Pr_2 (91%). – (k) Tetrazole, MeCN; *t*BuO_2H; Pd/C, H_2, MeOH; NEt_3(32%). – (l) NaOMe, MeOH; LiOH (67%).

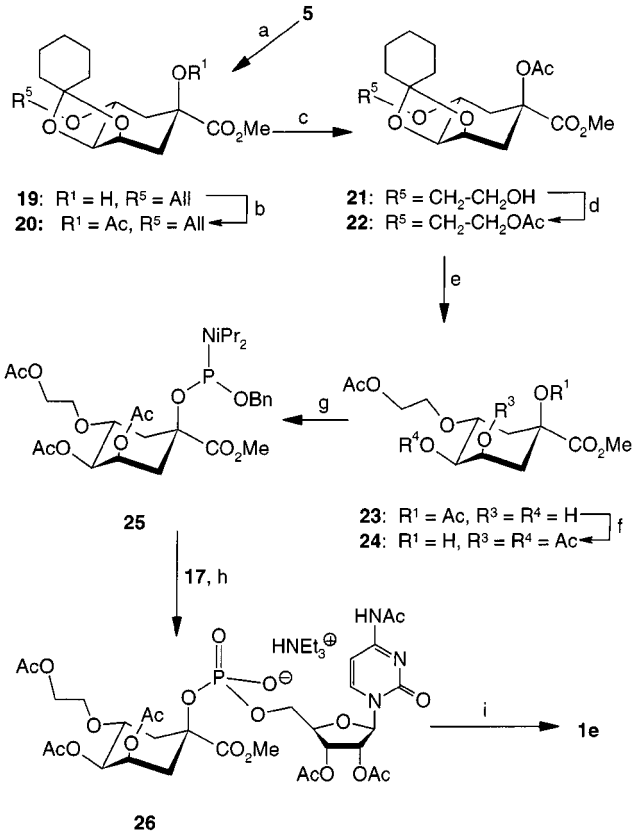
the *O*- and *N*-acyl protective groups under Zemplén conditions[18] and then methyl ester saponification with sodium hydroxide afforded target molecule **1e** as the disodium salt in 50% yield.

Synthesis of Transition State Analogues 2–4

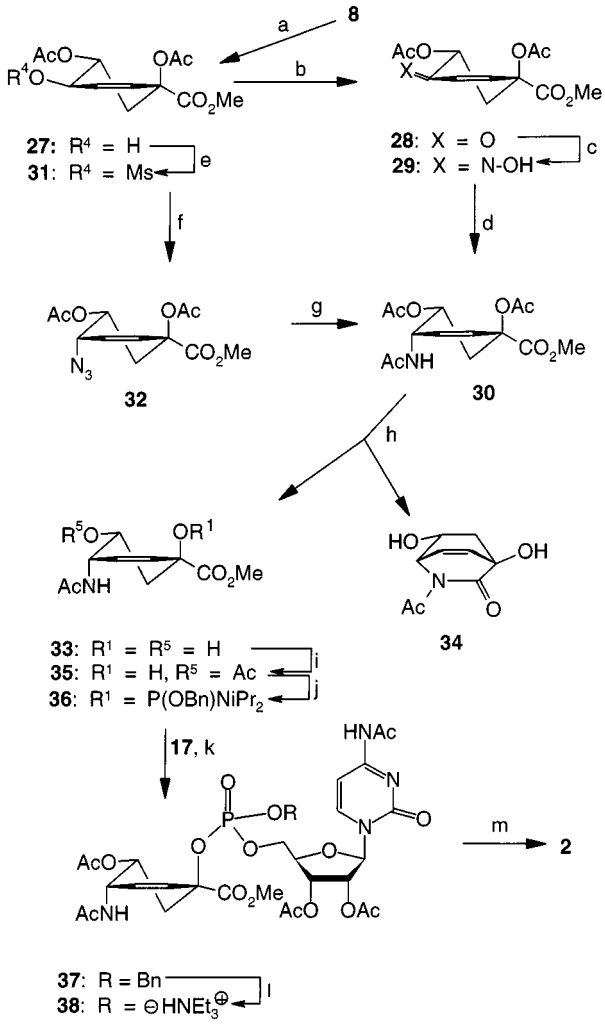
The introduction of a 2,3-C=C double bond into quinic acid in order to arrive at target molecule **2** could be readily accomplished with cyclic sulfate **8** (Scheme 5): treatment of **8** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at 80 °C led to 2,3-elimination; the generated 4-*O*-hydrogen sulfate group could be readily removed under aqueous acid conditions providing **27** in 88% yield. Oxidation of the liberated 4-hydroxy group with periodinane[21] afforded ketone **28**, which was transformed into oxime **29**. Ensuing reduction of **29** with zinc in acetic acid/acetic anhydride afforded the desired 4-acetylamino derivative **30**, though in only 24% yield. Therefore, compound **27** was transformed into mesylate **31** by treatment with methanesulfonyl chloride in pyridine; immediate reaction with lithium azide in DMF at 70 °C furnished azido derivative **32**. Dithiothreitol (DTT) reduction in aqueous pyridine in the presence of triethylamine and then treatment with acetic anhydride in pyridine afforded **30** in very good overall yield.

The structural assignment of **30** and **32** can be derived from the ^{1}H-NMR data; **32**: $J_{2,3}$ = 9.9, $J_{3,4}$ = 5.5, $J_{4,5}$ = 4.1 Hz. On de-*O*-acetylation of **30** under Zemplén conditions,[18] we not only obtained the desired **33**, but also lactam **34** as by-product, thus supporting the structural assignments (yield: 93%; **33/34** = 3:2). Immediate treatment of **33** with acetic anhydride in pyridine and catalytic amounts of DMAP afforded 1-*O*-unprotected derivative **35**. The same procedure as described for **16**, namely phosphitylation to give **36** and then reaction with **17** in the presence of tetrazole, followed by oxidation with *tert*-butyl hydroperoxide to give phosphate **37** and then hydrogenolytic debenzylation afforded protected target molecule **38**. Removal of the *O*- and *N*-acetyl groups under Zemplén conditions[18] and then methyl ester hydrolysis with sodium hydroxide in aqueous methanol furnished target molecule **2** as disodium salt in 69% yield.

Quinic acid transformation into **39** (Scheme 6) having an α,β-unsaturated ketone moiety and reduction of the keto group to afford compound **40** has been already performed by Shing and Tang.[14] Mitsunobu reaction[22] of **40** with benzoic acid as a nucleophile, furnished **41** with a pseudo-axial 3-benzoyloxy group. De-*O*-cyclohexylidenation with aqueous acetic acid led to **42**, which on de-*O*-acylation under Zemplén conditions,[18] ester hydrolysis with sodium hydroxide, and then acetylation with acetic anhydride, furnished acid **43**. Formation of a mixed anhydride by treatment with ethyl chloroformate in the presence of *N*-methylpiperidine (NMP) as base, and then reaction with *N,O*-dimethyl-hydroxylamine afforded Weinreb[23] amide **44**, which gave the formyl derivative **45**, on careful monitoring of the reduction with sodium dihydro-bis(2-methoxyethoxy)-



Scheme 4. Synthesis of **1e**. Reagents and conditions: (a) All–O–C(=NH)CCl_3, TFOH (90%). – (b) Ac_2O, Pyr, DMAP (82%). – (c) Ozone, MeOH/CH_2Cl_2, –78 °C; $NaBH_4$, –78 °C→ room temp. (73%). – (d) Ac_2O, Pyr (92%). – (e) HOAc/H_2O (qu). – (f) NaOMe, MeOH; Ac_2O, Pyr (70%). – (g) ClP(OBn)N*i*Pr_2, EtN*i*Pr_2 (65%. – (h) Tetrazole, MeCN; *t*BuO_2H; Pd/C, H_2, MeOH; NEt_3 (62%). – (i) NaOMe, MeOH; NaOH, MeOH/H_2O (59%).



Scheme 5. Synthesis of **2**. Reagents and conditions: (a) DBU, THF, 70 °C; H_2SO_4/H_2O (88%). – (b) Periodinane (83%). – (c) H_2N–OH (qu). – (d) Ac_2O/HOAc, Zn (24%). – (e) MsCl, Pyr. – (f) LiN_3, DMF, 70 °C (84%, two steps). – (g) DTT, Pyr/H_2O; Ac_2O, Pyr (87%). – (h) NaOMe, MeOH (**33**: 59%, **34**: 34%). – (i) Ac_2O, Pyr, DMAP (62%). – (j) ClP(OBn)N*i*Pr_2, EtN*i*Pr_2, MeCN. – (k) Tetrazole, MeCN; *t*BuO_2H; NEt_3 (31%, 2 steps). – (l) Pd/C, H_2, MeOH; NEt_3 (84%). – (m) NaOMe, MeOH; NaOH, MeOH (69%).

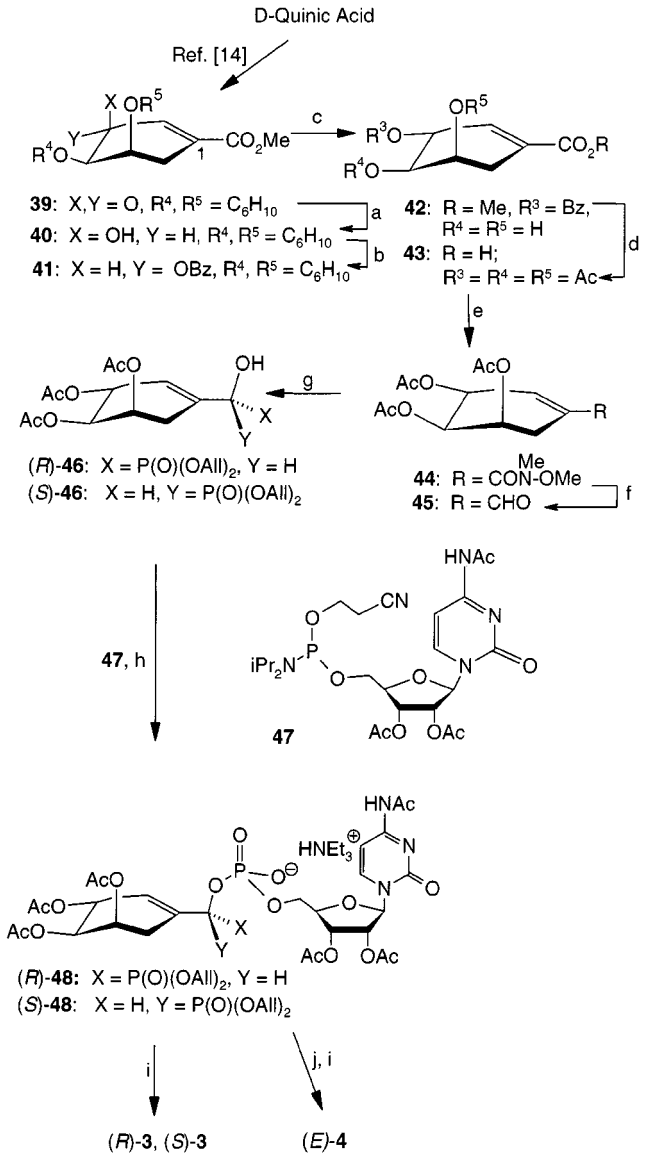
aluminate (RedAl) in toluene/THF at –60 °C. Reaction of **45** with diallyl hydrogen phosphonate[24] in the presence of triethylamine as a base, afforded a 1:1-mixture of diallyl phosphonates (*R*)- and (*S*)-**46** in 92% yield, which could be separated by MPLC chromatography. (*R*)- and (*S*)-**46** were treated with known cytidine-phosphite derivative **47**[25] in the presence of tetrazole; subsequent oxidation of the reaction product with *tert*-butyl hydroperoxide and then addition of triethylamine in order to remove the cyanoethyl group led to protected target molecules (*R*)-**48** and (*S*)-**48**, respectively, in high yields. De-*O*-allylation with catalytic $Pd(PPh_3)_4$ and dimedone as the nucleophile,[26] ensuing deacylation with aqueous ammonia, and then ion exchange gave target molecules (*R*)-**3** and (*S*)-**3** as the trisodium salts in high yields.

Treatment of (*R*)-**48** and (*S*)-**48**, or a mixture of the two, with DBU at 70 °C led to acetic acid elimination. Finally, reaction with acetic anhydride in pyridine in order to ensure complete *O*-acylation, then de-*O*-allylation, deacylation, and ion exchange as described above, led exclusively to the (*E*)-isomer of diene **4** in 34% yield; (*E*)-**4** was isolated as the trisodium salt.

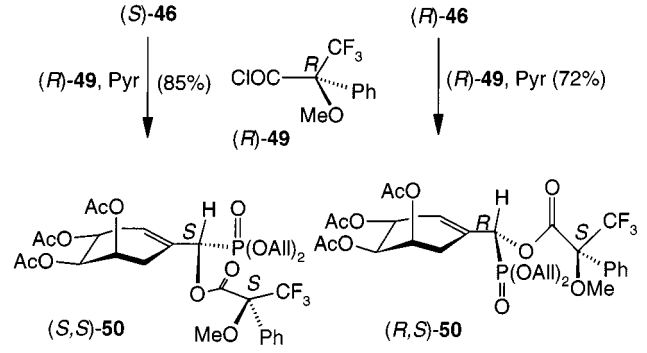
The structural assignments were essentially based on the NMR data. For the configurational assignment of (*R*)- and (*S*)-**46**, the Dale–Mosher method[27] was employed (Scheme 7). To this end, (*R*)- and (*S*)-**46** were treated with the (*R*)-isomer of α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[24] (MTPA-Cl) (*R*)-**49** which gave in the presence of pyridine the two diastereoisomers (*R,S*)- and (*S,S*)-**50**. Based on the generally accepted model for Mosher esters[28,29] (Scheme 7), the downfield shift of the methoxy group in the ^1H NMR ($\Delta\delta$ = 0.15 ppm) is associated with the (*R,S*)-isomer and also the downfield shift of the phosphorous atom in the ^{31}P NMR ($\Delta\delta$ = 0.48 ppm). The configurational assignment of **4** is based on ^{31}P-^{13}C coupling observed in the ^{13}C NMR: Coupling with C-2′′ is 11 Hz and coupling with C-6′′ is ca. 0 Hz, thus (*E*)-configuration for **4** is derived.

Determination of the K_i Values of 1–4

Measurement of the K_i values of compounds **1–4** is based on a previously reported sialyltransferase assay system.[3]



Scheme 6. Synthesis of (*R*)- and (*S*)-**3** and (*E*)-**4**. Reagents and conditions: (a) $NaBH_4$ MeOH [ref. 14]. – (b) DIAD, PPh_3, BzOH, THF (94%). – (c) HOAc, H_2O, 70 °C (94%). – (d) NaOMe, MeOH; NaOH, H_2O; Ac_2O, Pyr (83%). – (e) EtOC(O)Cl, NMP; MeNH(OMe), CH_2Cl_2, –20 °C (73%). – (f) RedAl, Tol/THF, –60° (60%). – (g) $HP(O)(OAll)_2$; NEt_3, CH_2Cl_2 (92%), (*R*)/(*S*)-**46** 1:1). – (h) Tetrazole, CH_2Cl_2; *t*BuO_2H; NEt_3 [(*R*)-**48**: 91%; (*S*)-**48**: 87%]. – (i) $Pd(PPh_3)_4$, Dimedone, THF; NH_3, H_2O; IR-120(Na^+) [(*R*)-**3** = (*S*)-**3** = 88%]. – (j) DBU, THF, 70 °C; Ac_2O, Pyr; then (i) (34%)



Scheme 7. Configurational assignment of **46**

As can be seen in Table 1, the previously obtained donor substrate analogues **1a** and **b**[3] exhibit comparable affinity to α(2–6)-sialyltransferase from rat liver (E.C. 2.4.99.1) as the natural substrate CMP-Neu5Ac. However, introduction of an equatorial amino group into the 3′′-position as in **1c**, unexpectedly, reduced binding by almost two orders of magnitude. This dramatic effect could be only partly compensated by replacing the equatorial hydroxy group in **1c** by an acetylamino group as in **1d**. However, attachment of a simple hydroxyethyl group at the 5′′-oxygen of the quinic acid moiety as in **1e** led to greatly improved binding which even surpasses the natural substrate. Yet, none of these compounds exhibited strong inhibition. This was immediately changed when a double bond was introduced in the quinic acid moiety, thus mimicking the potential transition state of the enzymatic sialyl transfer.[5,6] Compound **2** already exhibited a threefold higher binding to α(2–6)-sialyltransferase than CMP-Neu5Ac. Particularly interesting results were shown by (*R*)- and (*S*)-**3**, which are derived from our previous transition state model;[5,6] without changing the 3,4,5-trihydroxy group pattern of the quinic acid moiety, excellent inhibition properties were observed and even elimination product (*E*)-**4** exhibited better binding than CMP-Neu5Ac. Interesting leads for further studies were thus provided.

Table 1. Affinity of CMP-Neu5Ac (K_M) to α(2–6)-sialyltransferase of rat liver and inhibitions constants (K_i) of **1a–e**, **36**, (*R*)-**46**, (*S*)-**46**, and (*E*)-**47**

	K_M [μm]	K_i [μm]	Inhibition mode	K_M/K_i	Ref.
CMP-Neu5Ac	46	–	–	–	[3]
1a	–	44 ± 7	Competitive	1	[3]
1b	–	84 ± 14	Competitive	0.5	[3]
1c	–	1.400 ± 300	Competitive	0.03	[3]
1d	–	200 ± 20	Competitive	0.23	–
1e	–	20 ± 4	Competitive	2	–
2	–	15 ± 3	Competitive	3	–
(*R*)-**3**	–	1.6 ± 0.4	Competitive	30	–
(*S*)-**3**	–	0.27 ± 0.08	Competitive	170	–
(*E*)-**4**	–	10 ± 3	Competitive	5	–

Experimental Section

General: Solvents were purified according to the standard procedures. – Melting points (uncorrected): metal block. – NMR (22 °C, TMS or the resonance of the deuterated solvent was used as internal standard; solvents: $CDCl_3$, δ = 7.24; CD_3OD, δ = 3.315; D_2O, δ = 4.63; for ^{31}P NMR phosphoric acid was used as external standard; ^{31}P-NMR spectra were broadband ^1H decoupled): Bruker AC 250 Cryospec, Bruker DRX600, Jeol JNM-GX 400. – MALDI-MS: Kratos Kompact Maldi 1, 2,5-dihydroxybenzoic acid (DHB) or 6-aza-2-thiothymine (ATT) were used as matrices. – FAB-MS: Finnigan MAT 312/AMD 5000; 790 eV, 70 °C. – Optical rotations: Perkin–Elmer polarimeter 241/MS; 1 dm cell; 20 °C. – Thin-layer Chromatography: Merck plastic plates, silica gel 60 F_{254} or Merck glass plates, RP-18; detection by treatment with a solution of $(NH_4)_6Mo_7O_{24} \cdot 4\ H_2O$ (20 g) and $Ce(SO_4)_2$ (0.4 g) in 10% sulfuric acid (400 mL). – Flash chromatography: J.T. Baker silica gel 60 (0.040–0.063 mm) at a pressure of 0.3 bar. – Preparative

HPLC separations were performed with an Autochrom System with a Shimadzu LC 8A preparative pump and a Rainin Dynamax UV 1 detector at 254 nm. The column used was a Lichrosorb RP-18, 7 μm, 250 mm × 16 mm (Knauer GmbH, Germany). Mixtures of acetonitrile and 0.05 M triethylammonium bicarbonate (TEAB) (pH 7.2–7.5) were used as the mobile phase.

Methyl 3,4-*O*-Cyclohexylidenequinate (5): Compound **5** was synthesised according to a published procedure.[14]

Methyl 3,4-*O*-Cyclohexylidene-1,5-di-*O*-acetylquinate (6): To a solution of the protected methyl quinate **5** (4.7 g, 16.4 mmol) in dry pyridine (10 mL) and acetic anhydride (5 mL), a catalytic amount of DMAP was added. After stirring 15 h at room temp., the solution was coevaporated with toluene (3 × 60 mL). Flash chromatography (toluene/acetone, 10:1) of the crude product afforded the diacetate **6** as colourless syrup (6.05 g, quant.). – TLC (toluene/acetone, 10:1): R_f = 0.26; $[\alpha]_D$ = –32.3 (c = 2, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.53–1.74 (m, 10 H, cyclohexylidene), 2.05/2.07 (2s, 6 H, 2 Ac), 2.28–2.38 (m, 3 H, 2ax-, 6ax-, 6eq-H), 2.83 (ddd, ^2J =16.1 Hz, $^3J_{2eq,3}$ = $^4J_{2eq,6ed}$ = 2.5 Hz, 1 H, 2eq-H), 3.7 (s, 3 H, COOMe), 4.04 (dd, $J_{4.5}$ = 7.5 Hz, $J_{4,3}$ = 5.6 Hz, 1 H, 4-H), 4.40 (ddd, $J_{3,4}$ = 5.6 Hz, $J_{3,2ax}$ = 4.9 Hz, $J_{3,2eq}$ = 2.5 Hz, 1 H, 3-H), 5.26 (ddd, $J_{5,6ax}$ = 11.5 Hz, $J_{5,4}$ = 7.5 Hz, $J_{5,6eq}$ = 4.4 Hz, 1 H, 5-H). – $C_{18}H_{26}O_8$ (370.4): calcd. C 58.37, H 7.07; found C 58.54, H 7.00.

Methyl 1,5-Di-*O*-acetylquinate (7): A solution of the peracetylated compound **6** (3 g, 8.1 mmol) in dry dichloromethane (80 mL) was cooled to 0 °C. 5 equiv. ethanthiol (2.48 g, 40.5 mmol) and 0.15 equiv. *p*-toluenesulfonic acid (230 mg, 1.21 mmol) were added. The mixture was stirred for 16 h at 0–4 °C. The reaction mixture was neutralised with triethylamine, concentrated under vacuum, and the residue was extracted with petroleum ether ether (20 mL) to remove the dithioacetale. The petroleum ether was decanted, and the crude product was purified by flash chromatography (toluene/acetone, 4:1→2:1) to give the diol as a colourless oil (1.7 g,72%) with minor contaminations of the acetyl migrated product. – TLC (toluene/acetone, 2:1): R_f = 0.2. The NMR spectra corresponded with the published data.[30]

Methyl 1,5-Di-*O*-acetyl-3,4-*O*-sulfonylidenequinate (8):· A solution of diol **7** (1.1 g, 3.8 mmol) and triethylamine (2.1 mL, 15.2 mmol) in dry dichloromethane (30 mL) was cooled to 0 °C. Over a period of 20 min, thionyl chloride (1 mL, 13.35 mmol) dissolved in dichloromethane (3 mL) was added. After further 10 min at 0 °C, diethyl ether (20 mL) and water (20 mL) were added to the dark red solution. The organic phase was washed with water (2 × 20 mL) and the combined aqueous layers were extracted with diethyl ether (40 mL). The organic layers were dried ($MgSO_4$) and concentrated under vacuum. After drying under high vacuum for 1 h, the yellow foam was dissolved in ethyl acetate/acetonitrile 1:1 (50 mL) and was cooled to 0 °C. Then, water (40 mL), a catalytic amount of $RuCl_3 \cdot H_2O$, and sodium metaperiodate (1.6 g, 7.6 mmol) were added. After 40 min of stirring at 0 °C and 20 min at room temp., diethyl ether (80 mL) was added. The aqueous phase was extracted with diethyl ether (2 × 80 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and the filtrate was concentrated. Purification of the residue by flash chromatography (toluene/acetone, 6:1) afforded the cyclic sulfate **8** as a colourless amorphous solid (0.91 g, 68%). TLC (toluene/acetone, 6:1): R_f = 0.28, $[\alpha]_D$ = –33.4 (c = 1, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.78 (dd, $^3J_{6ax,5}$ = 11 Hz, ^2J = 13.9 Hz, 1 H, 6ax-H), 2.08/2.12 (2 s, 6 H, Ac), 2.55 (dd, $^3J_{2ax,3}$ = 4.6 Hz, ^2J = 16.9 Hz, 1 H, 2ax-H), 2.6 (ddd, $^4J_{6eq,2eq}$= 2.6, $^3J_{6eq,5}$ = 4.9 Hz, ^2J = 13.9 Hz, 1 H, 6eq-H), 3.07 (ddd, $^4J_{2eq,6eq}$ = 2.6, $^3J_{2eq,3}$ = 3.1 Hz, ^2J = 16.9 Hz, 1 H, 2eq-H), 3.73 (s, 3 H, COOMe), 4.86 (dd, $^3J_{4,3}$ = 5.5 Hz, $^3J_{4,5}$ = 7.8 Hz, 1 H, 4-H), 5.35 (ddd, $^3J_{3,2eq}$ = 3.1 Hz, $^3J_{3,2ax}$ = 4.6 Hz, $^3J_{3,4}$ = 5.5 Hz, 1 H, 3-H), 5.66 (ddd, $^3J_{5,6eq}$ = 4.9 Hz, $^3J_{5,6ax}$ = 11 Hz, $^3J_{5,4}$ = 7.8 Hz, 1 H, 5-H). – $C_{12}H_{16}O_{10}S$ (352.3): calcd. C 40.91, H 4.58; found C 41.07, H 4.67.

Methyl (1*R*,3*S*,4*R*,5*R*)-1,5-Di-*O*-acetyl-4-azido-1,3,5-trihydroxycyclohexane-1-carboxylate (9) and Methyl (1*S*,3*S*,4*S*,5*R*)-1,5-Di-*O*-acetyl-3-azido-1,4,5-trihydroxycyclohexane-1-carboxylate (10): To a solution of the cyclic sulfate **8** (1 g, 2.84 mmol) in DMF (35 mL) was added lithium azide (278 mg, 5.68 mmol). After stirring for 30 min at 80 °C, the solvent was removed under high vacuum. The residue was dissolved in THF (40 mL) and conc. sulfuric acid (60 μL) and water (70 μL) were added. The mixture was stirred for 30 min at room temp. and then solid sodium bicarbonate was added. The suspension was stirred until neutral, filtered over Celite, and the filtrate concentrated under vacuum. Flash chromatography (toluene/acetone, 8:1) of the residue afforded a mixture of the diastereomeric azides as a colourless oil. Separation by MPLC (toluene/ethyl acetate, 3:1) gave the pure products **10** (561 mg, 62%) as a colourless oil and **9** (224 mg, 25%) as a colourless oil that crystallised on standing.

9: m.p. 105–106.5 °C, TLC (toluene/acetone, 8:1): R_f = 0.23, $[\alpha]_D$ = –22.5 (c = 1, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.07/2.08 (2 s, 6 H, 2 Ac), 2.10–2.40 (m, 4 H, 2ax-, 2eq, 6ax, 6eq-H), 3.72 (s, 3 H, COOMe), 3.88 (dd, $J_{4,3}$ = 5.6 Hz, $J_{4,5}$ = 3.1 Hz, 1 H, 4 H), 4.17 (dd, $J_{3,2ax}$ = 8.9 Hz, $J_{3,4}$ = 5.6 Hz, 1 H, 3-H), 5.42 (ddd, $J_{5,6a}$ = 8.46 Hz, $J_{5,6b}$ = 5.6 Hz, $J_{5,4}$ = 3.1 Hz, 1 H, 5-H). – $C_{12}H_{17}N_3O_7$ (315.3): calcd. C 45.72, H 5.43, N 13.33; found C 45.89, H 5.41, N 13.06.

10: TLC (toluene/acetone, 8:1): R_f = 0.3, $[\alpha]_D$ = 2.9 (c = 1, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.70–1.86 (m, 2 H, 2ax-, 6ax-H), 2.06/2.11 (2 s, 6 H, 2 Ac), 2.4–2.6 (m, 2H, 2eq-, 6eq-H), 2.65 (br. s, 1 H, 4-OH), 3.53 (dd, $J_{4,3}$ = $J_{4,5}$ = 9.5 Hz, 1 H, 4-H), 3.6 (m, 1 H, 3-H), 3.70 (s, 3 H, COOMe), 4.92 (ddd, $J_{5,6ax}$ = 11.8 Hz, $J_{5,4}$ = 9.5 Hz, $J_{5.6eq}$ = 4.8 Hz, 1 H, 5-H).

Methyl (1*S*,3*S*,4*S*,5*R*)-1,5-Di-*O*-acetyl-1,4,5-trihydroxy-3-(trifluoroacetamido)cyclohexane-1-carboxylate (11): To a solution of azide **10** (1.24 g, 3.9 mmol) in dry ethyl acetate (40 mL) was added 10% Pd/C (350 mg), trifluoroacetic acid anhydride (2.48 g, 11.8 mmol), and sodium bicarbonate (1 g). After two hours of hydrogenation, triethylamine (2 mL) was added and the suspension was stirred for additional 30 min. It was filtered through a bed of Celite and the filtrate was evaporated. Flash chromatography (toluene/acetone, 4:1) of the residue gave the trifluoroacetamide **11** as a colourless foam (1 g, 66%) besides 0.17 g of recovered starting material. – TLC (toluene/acetone, 4:1): R_f = 0.14, $[\alpha]_D$ = 4.8 (c = 1, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.91 (dd, ^2J = 13.9 Hz, $J_{6ax,5}$ = 11.3 Hz, 1 H, 6ax-H), 2.03 (dd, ^2J = 14.1 Hz, $J_{2ax,3}$ = 12.1 Hz, 1 H, 2ax-H), 2.07/2.14 (2 s, 6 H, 2 Ac), 2.55–2.65 (m, 2 H, 2,6ax-H), 2.85 (br. s, 1 H, 4-OH), 3.65 (dd, $J_{4,3}$ = $J_{4,5}$ = 9.0 Hz, 1 H, 4-H), 3.71 (s, 3 H, COOMe), 4.12–3.98 (m, 1 H, 3-H), 4.99 (ddd, $J_{5,6ax}$ = 11.3 Hz, $J_{5,4}$ = 9.0 Hz, $J_{5,6eq}$ = 4.5 Hz, 1 H, 5-H), 6.84 (br. d, $J_{NH,3}$ = 7.1 Hz, 1 H, NH). – $C_{14}H_{18}F_3NO_8 \cdot 0.5\,H_2O$ (385.3): calcd. C 42.65, H 4.86, N 3.55; found C 42.66, H 4.82, N 3.58.

Methyl (1*S*,3*S*,4*R*,5*R*)-1,5-Di-*O*-acetyl-1,4,5-trihydroxy-3-(trifluoroacetamido)cyclohexane-1-carboxylate (12): A solution of alcohol **11** (0.92 g, 2.4 mmol) in dry dichloromethane (40 mL) was cooled to –18 °C. Abs. pyridine (388 μL, 4.8 mmol) and Tf_2O (640 μL, 3.8 mmol) were added successively. After 20 min the mixture was quenched with sodium bicarbonate solution (40 mL), washed with

brine (40 mL), and the combined aqueous layers were extracted with diethyl ether (50 mL). The combined organic extracts were dried ($MgSO_4$), and evaporation of the solvent afforded the triflate as a yellow foam [TLC (toluene/acetone, 6:1): $R_f = 0.5$], which was used in the following reaction without further purification. The triflate was dissolved in dry acetonitrile (50 mL) and tetrabutylammonium nitrite (1.7 g, 6 mmol) was added. After 30 min the solvents were removed under vacuum. Flash chromatography (toluene/acetone, 6:1) of the residue yielded the inverted alcohol **12** as a colourless foam (482 mg, 52%), besides starting material (120 mg, 13%). – TLC (toluene/acetone, 6:1): $R_f = 0.32$, $[\alpha]_D = -2.9$ ($c = 1$, $CHCl_3$). – ^1H NMR (250 MHz, $CDCl_3$): δ = 1.8–2.4 (m, 4 H, 2eq-, 2ax-, 6eq-, 6ax-H), 2.07/2.13 (2 s, 6 H, 2 Ac), 3.71 (s, 3 H, COOMe), 4.09 (dd, $J_{4,5} = J_{4,3} = 2.5$ Hz, 1 H, 4-H), 4.26–4.37 (m, 1 H, 3-H), 5.02 (ddd, $J_{5,6ax} = 12$ Hz, $J_{5,6eq} = 4.8$ Hz, $J_{5,4} = 2.5$ Hz, 1 H, 5-H), 6.78 (br. d, $J_{NH,3} = 8.7$ Hz, 1 H, NH). – $C_{14}H_{18}F_3NO_8$ (385.3): calcd. C 43.64, H 4.71, N 3.64; found C 44.11, H 4.93, N 3.87.

Methyl (1*S*,3*S*,4*R*,5*R*)-1,5-Di-*O*-acetyl-4-azido-1,5-dihydroxy-3-(trifluoroacetamido)cyclohexane-1-carboxylate (13): The alcohol **12** (0.41 g, 1.06 mmol) was dissolved in dry dichloromethane (15 mL) and cooled to 0 °C. To the stirred solution, dry pyridine (170 μL, 2.12 mmol) and then Tf_2O (286 μL, 1.7 mmol) were added slowly. After 15 min at 0 °C the solution was stirred for 3 h at room temp. Sodium bicarbonate solution (15 mL) was added and the layers were separated. The organic layer was washed once with brine and the combined aqueous layers were extracted with diethyl ether (1 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the filtrate evaporated under vacuum. The triflate was obtained as a brown foam (TLC: toluene/acetone, 6:1, $R_f = 0.5$) which was used directly in the following reaction. It was dissolved in DMF (10 mL) and lithium azide (0.155 g, 3.18 mmol) was added. This suspension was stirred for 45 min at 60 °C, then the DMF was removed under high vacuum. Flash chromatography (toluene/acetone, 10:1) of the residue yielded the azide **13** (327 mg, 75%) as a colourless foam. – TLC (toluene/acetone, 4:1): $R_f = 0.48$, $[\alpha]_D = 10.1$ ($c = 1$, $CHCl_3$). – ^1H NMR (250 MHz, $CDCl_3$): δ = 1.89 (dd, $^2J = 13.8$ Hz, $J_{6ax,5} = 11.2$ Hz, 1 H, 6ax-H), 2.08/2.13 (2 s, 6 H, 2 Ac), 2.18 (dd, $^2J = 14$ Hz, $J_{2ax,3} = 11.8$ Hz, 1 H, 2ax-H), 2.54 (ddd, $^2J = 14$ Hz, $J_{2eq,3} = 4.3$ Hz, $^4J_{2eq,6eq} = 2.6$ Hz, 1 H, 2eq-H), 2.66 (ddd, $^2J = 13.8$ Hz, $J_{6eq,5} = 4.6$ Hz, $^4J_{6eq,2eq} = 2.6$ Hz, 1 H, 6eq-H), 3.71 (s, 3 H, COOMe), 3.72 (dd, $^3J_{4,3} = 10.3$ Hz, $^3J_{4,5} = 9.3$ Hz, 1 H, 4-H), 3.77–3.89 (m, 1 H, 3-H), 5.04 (ddd, $J_{5,6ax} = 11.2$ Hz, $J_{5,4} = 9.3$ Hz, $J_{5,6eq} = 4.6$ Hz, 1 H, 5-H), 6.72 (br. d, $J_{NH,3} = 7.7$ Hz, 1 H, NH). – $C_{14}H_{17}F_3N_4O_7$ (410.3): calcd. C 40.98, H 4.18, N 13.65; found C 40.79, H 4.24, N 13.35.

Methyl (1*S*,3*S*,4*R*,5*R*)-4-Acetamido-1,5-di-*O*-acetyl-1,5-dihydroxy-3-(trifluoroacetamido)cyclohexane-1-carboxylate (14): To a solution of azide **13** (0.27 g, 0.65 mmol) in methanol (35 mL) 10% Pd/C (80 mg) was added. After 30 min of hydrogenation, Ac_2O (1.5 mL) and pyridine (3 mL) were added, and the suspension was stirred overnight. The suspension was filtered over Celite and concentrated under vacuum. The residue was coevaporated with toluene three times and purification by flash chromatography (toluene/acetone, 4:1) afforded the acetamide **14** (0.20 g, 72%) as a colourless foam. – TLC (toluene/acetone, 4:1): $R_f = 0.08$, $[\alpha]_D = -32.5$ ($c = 1$, $CHCl_3$). – ^1H NMR (250 MHz, $CDCl_3$): δ = 1.8–2.0 (m, 1 H, 6ax-H), 1.88/2.03 (2 s, 6 H, 2 O-Ac), 2.05 (dd, $^2J = 13.7$ Hz, $J_{2ax,3} = 12$ Hz, 1 H, 2ax-H), 2.13 (s, 3 H, N-Ac), 2.50–2.66 (m, 2 H, 2,6eq-H), 3.68 (s, 3 H, COOMe), 4.13–4.33 (m, 2 H, 3,4-H), 5.03 (ddd, $J_{5,6ax} = 11.73$, $J_{5,4} = 10$ Hz, $J_{5,6eq} = 4.6$ Hz, 1 H, 5-H), 6.05 (br. d, $J_{NH,4} = 8.63$ Hz, 1 H, 4-NH), 8.52 (br. d, $J_{NH,3} = 8.5$ Hz, 1 H, 3-NH). – $C_{16}H_{21}F_3N_2O_8$ (426.4): calcd. C 45.08, H 4.96, N 6.57; found C 45.08, H 4.97, N 6.48.

Methyl (1*S*,3*S*,4*R*,5*R*)-4-Acetamido-5-*O*-acetyl-1,5-dihydroxy-3-(trifluoroacetamido)cyclohexane-1-carboxylate (15): To a solution of compound **14** (0.168 g, 0.40 mmol) in dry methanol (10 mL) 0.5 M sodium methoxide solution in dry methanol (0.5 mL) was added. After 2 h at room temp. the deacetylation was complete and the solution was neutralised by addition of Amberlite IR 120 (H^+). The resin was filtered off and the filtrate was concentrated. The residue was dissolved in dry ethyl acetate (10 mL), Ac_2O (47 μL, 0.49 mmol), dry pyridine (32 μL, 0.40 mmol), and a catalytic amount of DMAP were added. After stirring for 1 h at room temp. the solvents were removed and the residue coevaported three times with toluene. Purification by flash chromatography (toluene/acetone, 4:1) yielded the alcohol **15** (123 mg, 81%) as a colourless foam. – TLC (toluene/acetone, 1:1): $R_f = 0.5$, $[\alpha]_D = -27.8$ ($c = 1$, $CHCl_3$). – ^1H NMR (250 MHz, $CDCl_3$): δ =1.88–2.33 (m, 4 H, 2eq-, 2ax-, 6eq-, 6ax-H), 1.94/2.04 (2 s, 6 H, O-Ac, N-Ac), 3.72 (s, 1 H, 1 OH), 3.78 (s, 3 H, COOMe), 4.16 (ddd, $J_{4,5} = J_{4,3} = 10.6$ Hz, $J_{4,NH} = 8.6$ Hz, 1 H, 4-H), 4.23–4.37 (m, 1 H, 3-H), 5.25 (ddd, $J_{5,6ax} = 10.9$ Hz, $J_{5,4} = 10.6$ Hz, $J_{5,6eq} = 5$ Hz, 1 H, 5-H), 6.44 (br. d, $J_{NH,4} = 8.6$ Hz, 1 H, 4-NH), 8.05 (br. d, $J_{NH,3} = 7.7$ Hz, 3-NH). – $C_{14}H_{19}F_3N_2O_7$ (384.3): calcd. C 43.76, H 4.98, N 7.29; found C 43.76, H 5.07, N 7.44.

Phosphane 16: To a solution of alcohol **15** (123 mg, 0.32 mmol) in dry acetonitrile (5 mL) was added diisopropylethylamine[19] (120 μL, 0.7 mmol) and (benzyloxy)chloro(diisopropylamino)phosphane (175 mg, 0.64 mmol) under an argon atmosphere. The reaction mixture was stirred for 8 h and flash chromatography (toluene/acetone, 5:1) of the residue yielded the phosphitamide **16** (180 mg, 91%) as a colourless oil (mixture of diastereoisomers) with minor contaminations of the phosphitamide reagent. – TLC (toluene/acetone, 2:1): $R_f = 0.45$, ^1H NMR (250 MHz, $CDCl_3$): δ = 1.1–1.3 [m, 12 H, 2 $CH(CH_3)_2$], 1.7–2.0 (m, 8 H, 2ax-, 6ax-H, 3 Ac), 2.4–2.6 (m, 2 H, 2eq-, 6eq-H), 3.52/3.59 (2 s, 3 H, COOMe) 3.60–3.78 [m, 2 H, 2 $CH(CH_3)_2$], 3.99–4.20 (m, 1 H, 4-H), 4.20–4.40 (m, 1 H, 3-H), 4.22–4.70 (m, 2 H, CH_2–Ph), 5.12–5.33 (m, 1 H, 5-H), 5.83/5.94 (2 br. d, $J_{NH,4} = 8.6$ Hz, 4-NH), 7.22–7.39 (m, 5 H, Ph), 8.27/8.33 (2 br. d, $J_{NH,3} = 7.7$ Hz, 3-NH).

***N*-Acetyl-2′,3′-di-*O*-acetylcytidine (17):** Compound **17** was synthesized as previously described.[3]

Phosphate 18: To a solution of the phosphitamide **16** (180 mg, 0.29 mmol) and cytidine **17**[3,8] (121 mg, 0.33 mmol) in dry acetonitrile (5 mL) was added tetrazole (32 mg, 0.45 mmol) under an argon atmosphere. After stirring for 18 h, *t*BuOOH (3 M in toluene, 0.25 mL) was added, and the solution was stirred for 3 h. Then triethylamine was added and the solvents were evaporated under vacuum. The residue was purified by flash chromatography (toluene/acetone, 1:2) to yield the protected phosphate contaminated with a small amount of cytidine **17**. A suspension of this mixture and 10% Pd/C (15 mg) in methanol/ethyl acetate (1:1, 10 mL) was hydrogenated for 15 min. The suspension was neutralised with NEt_3, filtered through Celite and evaporated. Flash chromatography (ethyl acetate/methanol/NEt_3, 4:1 + 1%) of the residue and lyophylisation afforded the triethylammonium salt **18** (85 mg, 32%) as a colourless foam. – TLC (ethyl acetate/methanol, 3:1 + 1% NEt_3) $R_f = 0.14$, $[\alpha]_D = 13.9$ ($c = 1$, methanol). – ^1H NMR (250 MHz, [D_4]methanol): δ = 1.30 (t, $J = 7.3$ Hz, 9 H, NCH_2CH_3), 1.80–2.22 (m, 2 H, 2ax′′-, 6ax′′-H), 1.87/1.93/2.08/2.11/2.17 (5 s, 15 H, 5 Ac), 2.46–2.64 (m, 2 H, 6eq′′-, 2eq′′-H), 3.18 (q, $J = 7.3$ Hz, 6 H, NCH_2CH_3) 3.77 (s, 3 H, COOMe), 4.02

(dd, $J_{4'',3''} = J_{4'',5''} = 10.7$ Hz, 1 H, 4''-H), 4.24–4.44 (m, 4 H, 4'-, 5a,b'-, 3''-H), 5.26 (ddd, $J_{5'',4''} = J_{5'',6ax''} = 10.7$ Hz, $J_{5'',6eq''} = 4.8$ Hz, 1 H, 5''-H), 5.55 (dd, $J_{2',3'} = 5.2$ Hz, $J_{2',1'} = 4.35$ Hz, 1 H, 2'-H), 5.60 (dd, $J_{3',2'} = 5.2$ Hz, $J_{3',4'} = 4.9$ Hz, 1 H, 3'-H), 6.21 (d, $J_{1',2'} = 4.35$ Hz, 1 H, 1'-H), 7.52 (d, $J_{5,6} = 7.5$ Hz, 1 H, 5-H), 8.54 (d, $J_{6,5} = 7.5$ Hz, 1 H, 6-H). – ^{31}P NMR (161.7 MHz, [D$_4$]methanol): δ = –2.93. – MS (MALDI, negative mode, matrix: ATT): *m/z*: 814 [M – NHEt$_3$]$^-$. – $C_{35}H_{52}F_3N_6O_{17}P \cdot 2\,H_2O$ (916.8): calcd. C 44.12, H 5.92, N 8.82; found C 44.22, H 5.99, N 8.69.

Lithium Salt 1d: To a solution of the protected triethylammonium salt **18** (50 mg, 0.055 mmol) in dry methanol (5 mL) was added a sodium methoxide solution in dry methanol (0.5 M, 0.2 mL). After stirring for 5 h at room temp. the solution was neutralised with Amberlite IRC 176 (H$^+$), filtered, and evaporated. The residue was dissolved in water/methanol 1:1 (4 mL) and lithium hydroxide (40 mg) was added. After stirring for 20 h at room temp., the solution was evaporated and lyophilised from water. The mixture of a lactam and amine **1d** was separated using preparative HPLC (0.05 M triethylammoniumbicarbonate buffer). Ion exchange with Amberlite IR 120 (Li$^+$) yielded the lithium salt of **1d** (20 mg, 67%) as a colourless foam. Further purification could be achieved by precipitation with ethanol from water. – TLC (ethyl acetate/methanol/1 M $NH_4CH_3CO_2$, 1:1:1): R_f = 0.33, $[\alpha]_D$ = 2.8 (*c* = 0.4, H_2O). – ^{1}H NMR (600 MHz, D_2O): δ = 1.83 (dd, *J* = 14 Hz, $J_{6ax'',5''} = 10.3$ Hz, 1 H, 6ax''-H), 2.06 (m, 1 H, 2ax''-H), 2.09 (s, 3 H, N-Ac), 2.56 (m, 1 H, 6eq''-H), 2.66 (m, 1 H, 2eq''-H), 3.53 (ddd, $J_{3'',2ax''} = 13$ Hz, $J_{3'',4''} = 10.3$ Hz, $J_{3'',2eq''} = 3.9$ Hz, 1 H, 3''-H), 3.88 (dd, $^3J_{4'',3''} = {}^3J_{4'',5''} = 10.3$ Hz, 1 H, 4''-H), 3.98 (ddd, $J_{5'',4''} = J_{5'',6ax''} = 10.3$ Hz, $J_{5'',6eq''} = 4.3$ Hz, H, 5''-H), 4.18–4.22 (m, 1 H, 5a'-H), 4.23–4.28 (m, 2 H, 4'-, 5b'-H), 4.30–4.36 (m, 2 H, 2'-, 3'-H), 5.98 (d, $J_{1',2'} = 3.5$ Hz, 1 H, 1'-H), 6.11 (d, $J_{5,6} = 7.6$ Hz, 1 H, 5-H), 7.96 (d, $J_{6,5} = 7.6$ Hz, 1 H, 6-H). – ^{13}C NMR (150.9 MHz, D_2O): δ = 22.18 (Ac–CH_3), 36.79 (C-2''), 41.08 (C-6''), 50.05 (C-3''), 56.52 (C-4''), 64.45 (C-5'), 67.42 (C 5''), 69.16 (C-3'), 74.07 (C-2'), 80.7 (C-1''), 82.8 (C-4'), 89.22 (C-1'), 96.44 (C-6), 141.55 (C-5), 157.71(C-4), 166.14 (C-2), 175.49, 177.09 (2 C=O). – ^{31}P NMR (161.7 MHz, D_2O): δ = –3.37. – MS (MALDI, negative mode, matrix: ATT): *m/z*: 537 [M – Li]$^-$ 543.2 for $C_{18}H_{27}LiN_5O_{12}P$.

Methyl 5-*O*-Allyl-3,4-*O*-cyclohexylidenequinate (19): To a solution of compound **5**[14] (10 g, 34.9 mmol) in dry dichloromethane (20 mL) and dry cyclohexane (50 mL) was added allyl trichloroacetimidate (14.14 g, 69.8 mmol) and trifluoromethanesulfonic acid (0.2 mL) at 0 °C. After stirring for 2 h at 0 °C and 3 h at room temp. the reaction was quenched by addition of a sodium bicarbonate solution. Diethyl ether (50 mL) was added and the phases were separated. The organic phase was washed with sodium bicarbonate solution and water, dried with $MgSO_4$, and concentrated under vacuum. The resulting oil was suspended in hexane/toluene (1:1, 25 mL) and the precipitated trichloroacetamide was filtered off. The filtrate was concentrated and the residue was purified by flash chromatography (toluene/ethyl acetate, 10:1 → 5:1) to yield compound **19** (10.24 g, 90%) as a colourless oil. – TLC (toluene/ethyl acetate, 6:1): R_f = 0.17, $[\alpha]_D$ = –45.0 (*c* = 1 in $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.38 (m, 2 H, cyclohexylidene-H), 1.53–1.77 (m, 8 H, cyclohexylidene-H, 2.10–2.39 (m, 4 H, 2a-, 2b-, 6a-, 6b-H), 3.56 (s, 1 H, 1-OH), 3.76 (s, 3 H, COOMe), 3.79–3.88 (m, 1 H, C*H*$_2$CH=CH$_2$), 4.04 (dd, $J_{4,5} = 7$ Hz, $J_{4,3} = 5.5$ Hz, 1 H, 4-H), 4.06–4.30 (m, 3 H, 3-, 5-H, C*H*$_2$CH=CH$_2$), 5.1–5.3 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.82–5.90 (m, 1 H, CH$_2$C*H*=CH$_2$).

Methyl 1-*O*-Acetyl-5-*O*-allyl-3,4-*O*-cyclohexylidenequinate (20): To a solution of alcohol **19** (10.24 g, 31.4 mmol) in pyridine/acetic anhydride (2:1, 18 mL) a catalytic amount of DMAP was added. After stirring for 14 h at room temp., the solution was coevaporated three times with toluene. Purification of the residue by flash chromatography (toluene/ethyl acetate, 25:1 → 20:1) affords compound **20** (9.5 g, 82%) as a colourless oil which solidifies on standing. m.p. 68–70 °C, TLC (toluene/ethyl acetate, 8:1): R_f= 0.22, $[\alpha]_D$ = –20.3 (*c* = 1, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30–1.70 (m, 11 H, cyclohexylidene-H, 6a-H), 2.03 (s, 3 H, Ac), 2.24–2.37 (m, 2 H, 2a-,6b-H), 2.71 (ddd, ^2J = 16 Hz, $J_{2b,3} \approx {}^4J_{2b,6b} \approx 2.8$ Hz, 1 H, 2b-H), 3.71 (s, 3 H, COOMe), 3.80 (ddd, $J_{5,6a} = 11.3$ Hz, $J_{5,4} = 6.9$ Hz, $J_{5,6b} = 4.3$ Hz, 1 H, 5-H), 3.98 (dd, $J_{4,5} \approx J_{4,3} \approx 6.3$ Hz, 1 H, 4-H), 4.12–4.19 (m, 2 H, CH$_2$CH=C*H*$_2$), 4.37 (ddd, $J_{3,4} \approx J_{3,2a} \approx 5.5$ Hz, $J_{3,2b} = 3.2$ Hz, 1 H, 3-H), 5.13–5.32 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.82–5.96 (m, 1 H, CH$_2$C*H*=CH$_2$). – $C_{19}H_{28}O_7$ (368.4): calcd. C 61.94, H 7.66; found C 61.65, H 7.65.

Methyl 1-*O*-Acetyl-3,4-*O*-cyclohexylidene-5-*O*-(hydroxyethyl)quinate (21): A solution of allyl compound **20** (9 g, 24.4 mmol) in dichloromethane/methanol (1:1, 60 mL) was cooled to –78 °C. At this temperature, ozone was bubbled through the solution for 25 min until the blue colour stayed. After warming to –60 °C, sodium borohydride (1.8 g, 48.8 mmol) was added stepwise and the solution was allowed to come to 0 °C. The solution was concentrated under vacuum after 3 h. The resulting suspension was resolved in ethyl acetate and saturated ammonium chloride solution. The phases were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried with $MgSO_4$, concentrated, and the residue was purified by flash chromatography (toluene/acetone, 4:1) to yield the hydroxyethyl compound **21** (6.39 g, 73%) as a colourless oil. – TLC (toluene/acetone, 4:1): R_f = 0.14, $[\alpha]_D$ = –27.4 (*c* = 2, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30–1.70 (m, 11 H, cyclohexylidene-H, 6a-H), 2.04 (s, 3 H, Ac), 2.29 (ddd, ^2J = 16.1 Hz, $J_{6b,5} = 4.3$ Hz, $J_{6b,2b} = 2.7$ Hz, 1 H, 6b-H), 2.34 (dd, ^2J = 16.1 Hz, $J_{2a,3} = 4.8$ Hz, 1 H, 2a-H), 2.75 (ddd, ^2J = 16.1 Hz, $J_{2b,3} >> {}^4J_{2b,6b} >> 2.7$ Hz, 1 H, 2b-H), 3.64–3.84 (m, 5 H, CH_2CH_2OH, 5-H), 3.72 (s, 3 H, COOMe), 3.98 (dd, $J_{4,5} = 7.0$ Hz, $J_{4,3} = 5.9$ Hz, 1 H, 4-H), 4.38 (ddd, $J_{3,4} = 5.9$ Hz, $J_{3,2a} = 4.8$ Hz, $J_{3,2b} = 3.0$ Hz, 1 H, 3-H). – $C_{18}H_{28}O_8 \cdot 1\,H_2O$ (372.4) calcd. C 55.37, H 7.74; found C 55.87, H 7.30.

Methyl 5-*O*-(2-acetoxyethyl)-1-*O*-acetyl-3,4-*O*-cyclohexylidenequinate (22): To a solution of hydroxyethyl compound **21** (6.24 g, 16.75 mmol) in dry ethyl acetate (10 mL) was added pyridine/acetic anhydride (2:1, 15 mL). After stirring for about 12 h the solution was coevaporated three times with toluene. The residue was purified by flash chromatography (toluene/acetone, 10:1) to yield compound **22** (6.39 g, 92%) as a colourless oil, which solidifies on standing. m.p. 71–72 °C, TLC (toluene/acetone, 4:1): R_f = 0.48, $[\alpha]_D$ = –13.5 (*c* = 1, CH_2Cl_2). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30–1.70 (m, 11 H, cyclohexylidene-H, 6a-H), 2.04/2.06 (2 s, 6 H, 2 Ac), 2.27 (ddd, ^2J = 13.7 Hz, $J_{6b,5} = 4.3$ Hz, $J_{6b,2b} = 2.5$ Hz, 1 H, 6b-H), 2.32 (dd, ^2J = 16.1 Hz, $J_{2a,3} = 4.8$ Hz, 1 H, 2a-H), 2.75 (ddd, ^2J = 16.1 Hz, $J_{2b,3} \approx {}^4J_{2b,6b} \approx 2.8$ Hz, 1 H, 2b-H), 3.71 (s, 3 H, COOMe), 3.72–3.82 (m, 2 H, CH_2CH$_2$OAc, 5-H), 3.88–4.00 (m, 2 H, CH_2CH$_2$OAc, 4-H), 4.20 (dd, *J* = 4.5 Hz, *J* = 5.4 Hz, 2 H, CH$_2$CH_2OAc), 4.36 (ddd, $J_{3,4} = 5.6$ Hz, $J_{3,2a} = 4.8$ Hz, $J_{3,2b} = 3$ Hz, 1 H, 3-H). – $C_{20}H_{30}O_9$ (414.5) calcd. C 57.96, H 7.30; found C 57.79, H 7.25.

Methyl 5-*O*-(2-Acetoxyethyl)-1-*O*-acetylquinate (23): A solution of compound **22** (200 mg, 0.48 mmol) in acetic acid (90%, 10 mL) was stirred for 1 h at 60–70 °C. The acetic acid was removed under vacuum and the residue was purified by flash chromatography (toluene/acetone, 2:1) to afford **23** (160 mg, quant.) as a colourless

oil. – TLC (toluene/acetone, 2:1): R_f = 0.23, $[\alpha]_D$ = –29.3 (c = 1, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.60 (dd, ^2J = 13.5 Hz, $J_{6a,5}$ = 10.8 Hz, 1 H, 6a-H), 2.04/2.06 (2 s, 6 H, 2 Ac), 2.00–2.14 (m, 1 H, 2a-H), 2.45 (ddd, ^2J = 13.5 Hz, $J_{6b,5}$ = 4.0 Hz, $J_{6b,2b}$ = 2.9 Hz, 1 H, 6b-H), 2.68 (ddd, ^2J = 15.7 Hz, $J_{2b,3} \approx {}^4J_{2b,6b} \approx$ 3.1 Hz, 1 H, 2b-H), 3.52 (dd, $J_{4,5}$ = 9 Hz, $J_{4,3}$ = 3.4 Hz, 1 H, 4-H), 3.60–3.73 (m, 1 H, CH_2CH$_2$OAc), 3.70 (s, 3 H, COOMe), 3.75–3.88 (m, 2 H, CH_2CH$_2$OAc, 5-H), 4.08–4.33 (m, 3 H, CH$_2$CH_2OAc, 3-H). – $C_{14}H_{22}O_9 \cdot 0.25\ H_2O$ (334.3) calcd. C 49.63, H 6.69; found C 49.88, H 6.58.

Methyl 5-*O*-(2-Acetoxyethyl)-3,4-di-*O*-acetylquinate (24): To a solution of the diacetyl compound **23** (261 mg, 0.78 mmol) in dry methanol (10 mL) was added a solution of sodium methoxide in dry methanol (0.5 M, 0.5 mL). After 1.5 h at room temp. the solution was neutralised by addition of Amberlite IR 120 (H^+), and concentrated under vacuum. The residue was dissolved in dry ethyl acetate (10 mL), and acetic anhydride (94.5 μL, 1 mmol), pyridine (65 μL, 0.8 mmol), and a catalytic amount of DMAP were added. After stirring for about 12 h the solvents were removed under vacuum, and the residue was purified by flash chromatography (toluene/acetone, 4:1) to yield the selectively acetylated compound **24** (205 mg, 70%) as a colourless oil. – TLC (toluene/acetone, 2:1): R_f = 0.46, $[\alpha]_D$ = –38.1 (c = 1, $CHCl_3$) – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.94–2.21 (m, 4 H, 2a,b-, 6a,b-H), 2.04/2.06 (2 s, 9 H, 3 Ac), 3.71 (t, J = 4.8 Hz, 2 H, CH_2CH$_2$OAc), 3.76 (s, 3 H, COOMe), 3.93 (ddd, $J_{5,4} \approx J_{5,6a} \approx$ 9.1 Hz, $J_{5,6b}$ = 4.3 Hz, 1 H, 5-H), 4.03–4.20 (m, 2 H, CH$_2$CH_2OAc), 4.97 (dd, $J_{4,5}$ = 8.7 Hz, $J_{4,3}$ = 3.3 Hz, 1 H, 4-H), 5.39 (ddd, $J_{3,2a}$ = 4.9 Hz, $J_{3,4} \approx J_{3,2b} \approx$ 3.5 Hz, 1 H, 3-H). – $C_{16}H_{24}O_{10} \cdot 0.25\ H_2O$ (376.4) calcd. C 50.45, H 6.49; found C 50.59, H 6.48.

(Benzyloxy)(diisopropylamino)[methyl 5-*O*-(2-acetoxyethyl)-3,4-di-*O*-acetylquinate]phosphane (25): To a solution of the alcohol **24** (200 mg, 0.53 mmol) in dry acetonitrile (7 mL) was added diisopropylethylamine (190 μL, 1.11 mmol) and (benzyloxy)chloro(diisopropylamino)phosphane[19] (290 mg, 1.06 mmol). The solvents were removed under vacuum after 18 h stirring at room temp. and the residue was purified by flash chromatography (toluene/acetone, 12:1) to yield the phosphitamide **25** (210 mg, 65%) as a mixture of diastereoisomers. – TLC (toluene/acetone, 2:1): R_f = 0.70–^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.08–1.32 [m, 12 H, 2 CH(CH_3)$_2$] 1.96–2.19 (m, 2 H, 2a-, 6a-H), 1.97/2.02/2.04/2.05 (4 s, 9 H, 3 Ac), 2.39–2.52 (m, 2 H, 2b-, 6b-H), 3.48–3.53 (m, 1 H, CH_2CH$_2$OAc), 3.55–3.79 [m, 4 H, CH_2CH$_2$OAc, 2 CH(CH$_3$)$_2$, 5-H], 3.59/3.62 (2 s, 3 H, COOMe), 3.99–4.03/4.07–4.12 (2 m, 2 H, CH$_2$CH_2OAc), 4.48–4.71 (m, 2 H, CH_2Ph), 5.13–5.20 (m, 1 H, 4-H), 5.28–5.36 (m, 1 H, 3-H), 7.21–7.39 (m, 5 H, Ph).

Phosphate 26: To a solution of phosphitamide **25** (210 mg, 0.34 mmol) and cytidine **17**[3,8] (138 mg, 0.37 mmol) in dry acetonitrile (7 mL), tetrazole (38 mg, 0.54 mmol) was added under argon. After 4 h stirring at room temp. *t*BuOOH (0.11 mL, 0.61 mmol, 5.5 M in nonane) was added. After 1.5 h, 2–3 drops of triethylamine were added and then the solution was concentrated under vacuum. The residue was purified by flash chromatography (toluene/acetone, 2:1 → 1:1) and afforded 220 mg of a mixture of benzyl protected phosphate contaminated with cytidine **17**. This mixture was dissolved in methanol (15 mL) and Pd/C (10%, 40 mg) was added. After 25 min of hydrogenation at room temp. the catalyst was filtered off, triethylamine was added, and the solvent was removed under vacuum. The residue was purified by flash chromatography (ethyl acetate/methanol, 3:1 + 1% NEt_3) to yield compound **26** (190 mg, 62%) as a colourless lyophilisate. – TLC (ethyl acetate/methanol, 3:1+1% NEt_3): R_f = 0.13, $[\alpha]_D$ = 7.2 (c = 0.5, methanol). – ^{1}H NMR (250 MHz, [D$_4$]methanol): δ = 1.30 (t, J = 7.3 Hz, 9 H, NCH$_2$CH_3), 1.98/2.05/2.06/2.08/2.11/2.17 (6 s, 18 H, 6 Ac), 2.24–2.62 (m, 4 H, 2a,b′′-, 6a,b′′-H), 3.19 (q, J = 7.3 Hz, 6 H, NCH_2CH$_3$), 3.62–3.71 (m, 2 H, CH_2CH$_2$OAc), 3.74 (s, 3 H, COOMe), 3.76–3.85 (m, 1 H, 5′′-H), 4.11 (t, J = 5.0 Hz, 2 H, CH$_2$CH_2OAc), 4.09–4.15 (m, 1 H, 5a′-H),4.20–4.28 (m, 1 H, 5b′-H), 4.40 (m, 1 H, 4′-H), 5.17 (dd, $J_{4'',5''}$ = 5.3 Hz, $J_{4'',3''}$ = 3.2 Hz, 1 H, 4′′-H), 5.36–5.43 (m, 1 H, 3′′-H), 5.45–5.52 (m, 2 H, 2′-, 3′-H), 6.22 (d, $J_{1',2'}$ = 4.6 Hz, 1 H, 1′-H), 7.57 (d, $J_{5,6}$ =7.5 Hz, 1 H, 5-H), 8.46 (d, $J_{6,5}$ = 7.5 Hz, 1 H, 6-H). – ^{31}P NMR (161.7 MHz, [D$_4$]methanol): δ = –3.48 (s, phosphate). – MS (MALDI, negative mode, matrix: ATT): m/z: 806 [M – NHEt$_3$]$^-$. – $C_{37}H_{57}N_4O_{20}P \cdot 2\ H_2O$ (908.6) calcd. C 47.04, H 6.51, N 5.93; found C 47.12, H 6.40, N 6.01.

Phosphate 1e: To a solution of the triethylammonium salt of compound **26** (50 mg, 0.055 mmol) in dry methanol (3 mL) was added a solution of sodium methoxide in dry methanol (0.5 M, 0.5 mL). After 2 h the solution was neutralised with Amberlite IRC 176 (H^+) and evaporated. The residue was dissolved in methanol/water (1:1, 5 mL) and NaOH (1 M, 0.5 mL) was added. After stirring overnight the solution was neutralised with IRC 176 (H^+), the pH value was adjusted to 8 with NaOH, and the solvents were removed by lyophilisation. The residue was purified by a Biogel P2 column (25 × 2.5 cm, water, flow 25 mL/h) to afford compound **1e** (19 mg, 59%) as a colourless lyophilisate. – TLC (ethyl acetate/methanol/1 M $CH_3CO_2NH_4$, 1:1:1): R_f = 0.64, $[\alpha]_D$ = –21.0 (c = 1, H_2O). – ^{1}H NMR (600 MHz, D_2O): δ = 1.60–1.70 (m, 1 H, 2a′′-H), 1.90–2.05 (m, 1 H, 6a′′-H), 2.25–2.35 (m, 1 H, 6b′′-H), 2.50–2.60 (m, 1 H, 2b′′-H), 3.40–3.55 (m, 2 H, HOCH_2CH$_2$O, 4′′-H), 3.58–3.70 (m, 3 H, HOCH$_2$CH_2O), 3.78–3.88 (m, 1 H, 3′′-H), 4.00–4.10 (m, 2 H, 5a′-, 3′-H), 4.10–4.13 (m, 1 H, 4′-H), 4.16–4.25 (m, 3 H, 2′-, 5b′-, 5′′-H), 5.86 (d, $J_{1',2'}$ = 4.0 Hz, 1 H, 1′-H), 6.03 (d, $J_{5,6}$ = 7.5 Hz, 1 H, 5-H), 7.88 (d, $J_{6,5}$ = 7.5 Hz, 1 H, 6-H). – ^{13}C NMR (150.9 MHz, D_2O): δ = 38.3 (6′′-C), 38.5 (2′′-C), 62.2 (HOCH$_2$-CH$_2$O), 65.6 (d, $^2J_{C,P}$ = 5.3 Hz, 5′-H), 70.4 (2′-C), 70.7 (3′-C), 71.8 (HOCH$_2$CH$_2$O), 75.4 (5′′-C), 75.6 (4′′-C), 76.7 (3′′-C), 84.1 (d, $^3J_{C,P}$ = 7.9 Hz, 4′-H), 84.3 (1′′-C), 90.6 (1′-C), 97.8 (5-C), 142.9 (6-C), 158.9 (4-C), 167.4 (2-C), 175.54 (C=O). – ^{31}P NMR (161.7 MHz, D_2O): δ = –2.77 (s, phosphate). – MS (MALDI, negative mode, matrix: ATT): m/z: 538 [M – 2 Na + H]$^-$, 585.1 for $C_{18}H_{26}N_3Na_2O_{14}P$.

Methyl (1*R*,4*R*,5*R*)-1,5-Di-*O*-acetyl-1,4,5-trihydroxycyclohex-2-ene-1-carboxylate (27): To a solution of cyclic sulfate **8** (2 g, 5.67 mmol) in dry THF (50 mL) was added DBU (1.02 mL, 6.8 mmol) and the solution was heated for 30 min to 70 °C. The reaction mixture was cooled to room temp. and was treated with sulfuric acid (0.05 mL, 0.94 mmol) and water (0.1 mL) for 1 h to remove the sulfate group. Solid sodium bicarbonate and $MgSO_4$ were added, and the suspension was stirred until neutral. The suspension was filtered over Celite, the residue was washed carefully with acetone and the solvents were removed under vacuum. Flash chromatography (toluene/acetone, 6:1) of the residue yielded the eliminated product **27** (1.35 g, 88%) as a colourless foam. – TLC (toluene/acetone, 2:1): R_f = 0.48, $[\alpha]_D$ = 2.5 (c = 1, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.03 (dd, $J_{6a,6b}$ = 13.6 Hz, $J_{6a,5}$ = 12.2 Hz, 1 H, 6a-H), 2.07/2.10 (2 s, 6 H, 2 Ac), 2.42 (ddd, $J_{6b,6a}$ = 13.6 Hz, $J_{6b,5}$ = 4 Hz, $^4J_{6b,2}$ = 1.9 Hz, 1 H, 6b-H), 3.73 (s, 3 H, COOMe), 4.26 (ddd, $J_{4,5}$ = 8.2 Hz, $J_{4,3} \approx J_{4,2} \approx$ 2.2 Hz, 1 H, 4-H), 5.03 (ddd, $J_{5,6a}$ = 12.2 Hz, $J_{5,4}$ = 8.2 Hz, $J_{5,6b}$ = 4 Hz, 1 H, 5-H), 5.94 (dd, $J_{3,2}$ = 10.1 Hz, $J_{3,4}$ = 2.15 Hz, 1 H, 3-H), 6.13 (ddd, $J_{2,3}$ = 10.1 Hz, $^4J_{2,6b} \approx {}^4J_{2,4} \approx$ 2 Hz, 1 H, 2-H). – $C_{12}H_{16}O_7$ (272.3): calcd. C 52.94, H 5.92; found C 52.73, H 5.91.

Methyl (1*R*,5*R*)-1,5-Di-*O*-acetyl-1,5-dihydroxy-3-oxocyclohex-2-ene-1-carboxylate (28): To a solution of compound **27** (1.17 g, 4.22 mmol) in dry dichloromethane (60 mL), Dess–Martin periodinane was added (2.14 g, 5.06 mmol) and the white suspension was stirred for 30 min at room temp. Saturated sodium bicarbonate solution (100 mL) and sodium thiosulfate (15 g) were added and the mixture was stirred vigorously for 30 min. The phases were separated and the organic phase was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (toluene/acetone, 8:1) to afford the ketone **28** (0.94 g, 83%). – TLC (toluene/acetone, 4:1): R_f = 0.6. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.11/2.16 (2 s, 6 H, 2 Ac), 2.43 (dd, $^2J \approx J_{6a,5} \approx$ 13.0 Hz, 1 H, 6a-H), 2.67 (ddd, ^2J = 13.2 Hz, $J_{6b,5}$ = 5.3 Hz, $^4J_{6b,2}$ = 1.9 Hz, 1 H, 6b-H), 3.78 (s, 3 H, COOMe), 5.70 (dd, $J_{5,6a}$ = 12.7 Hz, $J_{5,6b}$ = 5.3 Hz, 1 H, 5-H), 6.16 (d, $J_{3,2}$ = 10.2 Hz, 1 H, 3-H), 7.30 (dd, $J_{2,3}$ = 10.2 Hz, $^4J_{2,6b}$ = 1,9 Hz, 1 H, 2-H).

Methyl (1*R*,5*R*)-1,5-Di-*O*-acetyl-1,5-dihydroxy-3-hydroxyliminocyclohex-2-ene-1-carboxylate (29): To a solution of ketone **28** (0.72 g, 2.67 mmol) in dry methanol (30 mL) were added hydroxyl ammonium chloride (0.28 g, 4 mmol) and pyridine (432 μL, 0.42 g, 5.34 mmol). After 2.5 h stirring at room temp. the solvent was removed under vacuum and the residue was purified by flash chromatography (toluene/acetone, 8:1) to afford a (*E*/*Z*)-mixture of the oxime **29** (0.76 g, quant.). – TLC (toluene/acetone, 2:1): R_f = 0.6. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.01/2.06/2.07/2.08 (4 s, 6 H, 4 Ac), 2.30–2.52 (m, 2 H, 6a,b-H), 3.74/3.76 (2 s, 3 H, 2 COOMe), 5.83/6.25 [2 dd, ($J_{5,6a}$ = 9.9 Hz, $J_{5,6b}$ = 4.7 Hz)/($J_{5,6a} >> J_{5,6b} >>$ 5.1 Hz), 1 H, 5-H], 6.37/7.00 (2 d, $J_{3,2}$ = 10.3 Hz, 1 H, 3-H), 6.51/6.60 (2 d, $J_{2,3}$ = 10.2 Hz, 1 H, 2-H). – MS (MALDI, positive mode, matrix: DHB): *m*/*z*: 307 $[M + Na]^+$, 441 $[M + DHB + H]^+$, 285.1 for $C_{12}H_{15}NO_7$.

Methyl (1*R*,4*S*,5*R*)-4-Acetamido-1,5-di-*O*-acetyl-1,5-dihydroxycyclohex-2-ene-1-carboxylate (30):

a) From Oxime 29: To a solution of oxime **29** (0.44 g, 1.54 mmol) in acetic anhydride/acetic acid (1.3:1, 30 mL), zinc powder (1.0 g) was added gradually at 0 °C. After 48 h stirring at room temp. the suspension was filtered, and the filtrate was coevaporated with toluene three times. The residue was purified by flash chromatography (toluene/acetone, 5:1) to yield a mixture of compound **30** (115 mg, 24%) and methyl 4-acetamidobenzoate (50 mg, 16%).

b) From Azide 32 by Catalytic Reduction with Lindlar Catalyst: To a solution of azide **32** (100 mg, 0.34 mmol) in methanol (5 mL) was added Lindlar catalyst (50 mg) and the suspension was hydrogenated for 45 min. Then acetic anhydride (0.5 mL) was added and the suspension was stirred for 2 h at room temp. The suspension was filtered over Celite and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (toluene/acetone, 2:1) to yield the acetamide **30** (50 mg, 47%) as a lightly yellow foam.

c) From Azide 32 by Reduction with Dithiothreitol (DTT): To a solution of azide **32** (370 mg, 1.25 mmol) in pyridine/water (4:1, 15 mL) were added triethylamine (0.5 mL) and DTT (563 mg, 3.54 mmol). After 1 h stirring at room temp. the solvents were removed under vacuum and the residue was coevaporated three times with toluene. The residue was dissolved in dry pyridine/acetic anhydride (2:1, 6 mL) and stirred for 15 h at room temp. After coevaporating three times with toluene the residue was purified by flash chromatography (toluene/acetone, 2:1) to afford acetamide **30** (340 mg, 87%) as a colourless foam. – TLC (toluene/acetone, 2:1): R_f = 0.2, $[\alpha]_D$ = 34.3 (*c* = 2, CH_2Cl_2). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.05/1.99/1.98 (3 s, 9 H, 3 Ac), 2.0–2.3 (m, 2 H, 6a,b-H), 3.73 (s, 3 H, COOMe), 4.80–4.91 (m, 1 H, 4-H), 5.22 (ddd, $J_{5,6a}$ = 11.1 Hz, $J_{5,4} \approx J_{5,6b} \approx$ 4.2 Hz, 1 H, 5-H), 5.54 (br. d, $J_{NH,4}$ = 5.5 Hz, 1 H, NH), 5.92 (dd, $J_{3,2}$ = 10 Hz, $J_{3,4}$ = 5 Hz, 1 H, 3-H), 6.23 (ddd, $J_{2,3}$ = 10 Hz, $^4J_{2,6a} \approx {}^4J_{2,4} \approx$ 1.2 Hz, 1 H, 2-H). – $C_{14}H_{19}NO_7$ (313.3) calcd. C 53.67, H 6.11, N 4.47; found C 53.21, H 6.15, N 4.81.

Methyl (1*R*,4*S*,5*R*)-1,5-Di-*O*-acetyl-4-azido-1,5-dihydroxycyclohex-2-ene-1-carboxylate (32): To a solution of alcohol **27** (0.6 g, 2.2 mmol) in dry dichloromethane (20 mL) were added triethylamine (368 μL, 2.64 mmol) and mesyl chloride (204 μL, 2.64 mmol) at 0 °C. After 20 min stirring at 0 °C, sodium bicarbonate solution (15 mL) was added, the phases were separated, and the organic phase was washed with brine. The combined aqueous phases were extracted two times with diethyl ether, and the combined organic phases were dried with $MgSO_4$. After removing the solvents under vacuum the mesylate (R_f = 0.6, toluene/acetone, 2:1) was dried under high vacuum. The crude mesylate **31** was dissolved in DMF (20 mL) and lithium azide (0.32 g, 6.51 mmol) was added. After 1 h at 70 °C the solution was concentrated under high vacuum, and the residue was dissolved in water (20 mL) and extracted three times with diethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (toluene/acetone, 10:1) to afford azide **32** (0.55 g, 84%) as a colourless oil. – TLC (toluene/acetone, 2:1): R_f = 0.74, $[\alpha]_D$ = 107.7 (*c* = 2, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.04/2.10 (2 s, 6 H, 2 Ac), 2.19 (dddd, $J_{6a,6b}$ = 13.6 Hz, $J_{6a,5}$ = 4.1 Hz, $^4J_{6a,2} \approx {}^4J_{6a,4} \approx$ 1 Hz, 1 H, 6a-H), 2.31 (dd, $J_{6b,6a}$ = 13.6 Hz, $J_{6b,5}$ = 11.8 Hz, 1 H, 6b-H), 3.72 (s, 3 H, COOMe), 4.25 (dd, $J_{4,3}$ = 5.5 Hz, $J_{4,5}$ = 4.1 Hz, 1 H, 4-H), 5.83 (ddd, $J_{5,6b}$ = 11.8 Hz, $J_{5,6a} \approx J_{5,4} \approx$ 4.1 Hz, 1 H, 5-H), 5.97 (dd, $J_{3,2}$ = 9.9 Hz, $J_{3,4}$ = 5.5 Hz, 1 H, 3-H), 6.34 (ddd, $J_{2,3}$ = 9.9 Hz, $^4J_{2,6} >> {}^4J_{2,4} >>$ 1 Hz, 1 H, 2-H). – $C_{12}H_{15}N_3O_6$ (297.3) calcd. C 48.49, H 5.09, N 14.13; found C 48.53, H 5.27, N 13.98.

(1*R*,4*S*,5*R*)-4-*N*-Acetyl-4-amino-1,5-dihydroxycyclohex-2-ene-1-carboxylic Acid 1,4-Lactam (34) and Methyl (1*R*,4*S*,5*R*)-4-Acetamido-5-*O*-acetyl-1,5-dihydroxycyclohex-2-ene-1-carboxylate (35): To a solution of compound **30** (320 mg, 1.03 mmol) in dry methanol (15 mL) was added a solution of sodium methoxide in dry methanol (0.5 M, 1.5 mL). After 1 h stirring at room temp. the solution was neutralised with Amberlite IR 120 (H^+) and concentrated under vacuum. Flash chromatography (toluene/acetone, 1:2) of the residue afforded the deacetylated compound **33** [139 mg, 59%, R_f = 0.11 (toluene/acetone, 1:1)] and the lactam **34** (60 mg, 34%). To a solution of deacylated **33** (139 mg, 0.61 mmol) in dry ethyl acetate (10 mL), was added acetic anhydride (72 μL, 0.76 mmol), pyridine (49 μL, 0.61 mmol), and a catalytic amount of DMAP. After 5 h stirring at room temp., methanol (1 mL) was added and the solvents were evaporated. The residue could be purified by crystallisation from toluene/acetone (1:1) to yield the selectively acetylated compound **35** (100 mg, 62%) as a colourless solid.

34: TLC (toluene/acetone, 1:2): R_f = 0.48, $[\alpha]_D$ = –235.4 (*c* = 0.5, methanol). – ^{1}H NMR (250 MHz, [D$_4$]methanol): δ = 1.99 (s, 3 H, N-Ac), 2.39 (d, $J_{6a,6b}$ = 11.1 Hz, 1 H, 6a-H), 2.58 (ddd, $J_{6b,6a}$ = 11.1 Hz, $^4J_{6b,5}$ = 6.2 Hz, $^4J_{6b,2} \approx$ 2.2 Hz, 1 H, 6b-H), 4.80–4.88 (m, 2 H, 4-, 5-H), 5.58 (ddd, $J_{3,2}$ = 9.8 Hz, $J_{3,4} \approx {}^4J_{3,5} \approx$ 2.5 Hz, 1 H, 3-H), 6.10 (ddd, $J_{2,3}$ = 9.8 Hz, $J_{2,6a} \approx J_{2,4} \approx$ 2.2 Hz, 1 H, 2-H). – MS (MALDI, positive mode, matrix: DHB): *m*/*z*: 199 $[M + H]^+$, 200 $[M + Na]^+$. – $C_9H_{11}NO_4 \cdot 1/8\ H_2O$ (197.19) calcd. C 54.20, H 5.69, N 7.0; found C 54.10, H 5.90, N 6.60.

35: TLC (toluene/acetone, 1:1): R_f = 0.3, $[\alpha]_D$ = 59.0 (*c* = 0.5, methanol). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.94 (dd, $J_{6a.6b}$ =

13.6 Hz, $J_{6a,5}$ = 3.5 Hz, 1 H, 6a-H), 1.99/2.00 (2 s, 6 H, 2 Ac), 2.36 (dd, $J_{6b,6a}$ = 13.6 Hz, $J_{6b,5}$ = 11.1 Hz, 1 H, 6b-H), 3.80 (s, 3 H, COOMe), 4.87 (ddd, $J_{4,5} \approx J_{4,3} \approx$ 4.6 Hz, $J_{4,NH}$ = 8.9 Hz, 1 H, 4-H), 5.27 (ddd, $J_{5,6b}$ = 11.1 Hz, $J_{5,4}$ = 4.5 Hz, $J_{5,6a}$ = 3.5 Hz, 1 H, 5-H), 5.43 (br. d, $J_{NH,4}$ =8.9 Hz, 1 H, NH), 5.79 (d, $J_{2,3}$ = 9.9 Hz, 1 H, 2-H), 5.89 (dd, $J_{3,2}$ = 9.9 Hz, $J_{3,4}$ = 4.8 Hz, 1 H, 3-H). – MS (MALDI, positive mode, matrix: DHB): *m/z*: 272 $[M + H]^+$, 295 $[M + Na]^+$, 311 $[M + K]^+$. – $C_{12}H_{17}NO_6 \cdot 0.5\ H_2O$ (271.27) calcd. C 51.43, H 6.47, N 5.00; found C 51.68, H 6.15, N 5.00.

Phosphane 36: To a solution of the alcohol **35** (70 mg, 0.25 mmol) in dry acetonitrile (7 mL), diisopropylethylamine (137 µL, 0.8 mmol) and (benzyloxy)chloro(diisopropylamino)phosphane[19] (199 mg, 0.73 mmol) were added. The solvents were removed under vacuum after 2.5 h stirring at room temp., and the residue was purified by flash chromatography (toluene/acetone, 5:1) to yield the phosphitamide **36** (120 mg) contaminated with the chlorophosphane. – TLC (toluene/acetone, 2:1): R_f = 0.38 (mixture of diastereoisomers). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.1–1.3 [m, 12 H, 2 CH(CH_3)$_2$], 1.90–2.10 (m, 1 H 6a-H), 1.96/1.97/1.98 (3 s, 6 H, 2 Ac), 2.49/2.70 (2 dd, $J_{6b,6a}$ = 14 Hz, $J_{6b,5}$ = 9 Hz, 1 H, 6b-H), 3.5–3.8 [m, 2 H, 2 C*H*(CH_3)$_2$], 3.65/3.66 (2 s, 3 H, COOMe), 4.5–4.7 (m, 2 H, CH_2Ph), 4.82–4.94 (m, 1 H, 4-H), 5.21–5.30 (m, 1 H, 5-H), 5.58–5.65 (m, 1 H, NH), 5.70–5.82 (m, 1 H, 3-H), 6.16/6.22 (2 dd, $J_{2,3}$ =10.1 Hz, $J_{2,6a}$ = 1.7 Hz, 1 H, 2-H), 7.20–7.40 (m, 5 H, Ph).

Phosphate 37: To a solution of phosphitamide **36** (120 mg) and cytidine **17** (144 mg, 0.39 mmol) in dry acetonitrile (3 mL), was added tetrazole (38 mg, 0.54 mmol) under argon. After 4 h stirring at room temp. *t*BuOOH (0.13 mL, 0.72 mmol, 5.5 M in nonane) was added. After 1.5 h 2–3 drops triethylamine were added and the solution was concentrated under vacuum. The residue was purified by flash chromatography (toluene/acetone, 1:1 → 1:2) to afford the protected phosphate **37** (62 mg, 31% over 2 steps) as a colourless oil. – TLC (toluene/acetone, 1:2): R_f = 0.15 (mixture of diastereoisomers) – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.90–2.10 (m, 1 H, 6a-H), 1.94/1.96/1.98/1.99/2.05/2.06/2.25 (7 s, 15 H, 5 Ac), 2.30–2.49 (m, 1 H, 6b-H), 3.76/3.77 (2 s, 3 H, COOMe), 4.12–4.41 (m, 3 H, 4′-, 5a,b′-H), 4.81–5.01 (m, 1 H, 4′′-H), 5.02–5.23 (m, 3 H, CH_2Ph, 5′′-H), 5.29–5.39 (m, 2 H, 2′-, 3′-H), 5.69/5.74 (2 d, $J_{NH,4''}$ = 8.9 Hz, 1 H, NH), 5.90/5.99 (2 dd, $J_{3'',2''}$= 10.0 Hz, $J_{3'',4''}$ = 4.5, 1 H, 3′′-H), 6.05/6.14 (2 d, $J_{1',2'}$ = 4.0 Hz, 1 H, 1′-H), 6.20–6.56 (m, 1 H, 2′′-H), 7.25–7.41 (m, 6 H, Ph, 5-H), 7.91/8.05 (2 d, $J_{6,5}$ = 7.6 Hz, 1 H, 6-H).

Phosphate 38: To a solution of the protected phosphate **37** in methanol (10 mL) was added Pd/C (10%, 10 mg). After 10 min of hydrogenation at room temp. the catalyst was removed by filtration over Celite, triethylamine was added, and the solvent was evaporated. The residue was purified by flash chromatography (ethyl acetate/methanol 3:1 + 1% NEt_3) to yield compound **38** (51 mg, 84%) as a colourless lyophilisate. – TLC (ethyl acetate/methanol 3:1 + 1% NEt_3): R_f = 0.12, $[\alpha]_D$ = 52.9 (*c* = 1, methanol). – ^{1}H NMR (250 MHz, [D_4]methanol): δ = 1.30 (t, *J* = 7.3 Hz, 9 H, NCH_2CH_3), 1.93/1.94/2.06/2.10/2.18 (5 s, 15 H, 5 Ac), 2.10–2.42 (m, 2 H, 6a,b′′-H), 3.20 (q, *J* = 7.3 Hz, 6 H, NCH_2CH_3), 3.77 (s, 3 H, COOMe), 4.06–4.25 (m, 2 H, 5a,b′-H), 4.39 (m, 1 H, 4′-H), 4.75–4.80 (m, 1 H, 4′′-H), 5.22–5.30 (m, 1 H, 5′′-H), 5.43–5.50 (m, 2 H, 2′-, 3′-H), 5.82 (dd, $J_{3'',2''}$ = 10.1 Hz, $J_{3'',4''}$ = 4.5 Hz, 1 H, 3′′-H), 6.18 (d, $J_{1',2'}$= 4.3 Hz, 1 H, 1′-H), 6.39 (d, $J_{2'',3''}$ = 10 Hz, 1 H, 2′′-H), 7.52 (d, $J_{5,6}$ =7.6 Hz, 1 H, 5-H), 8.43 (d, $J_{6,5}$ = 7.6 Hz, 1 H, 6-H). – ^{31}P NMR (161.7 MHz, [D_4]methanol): δ = –2.81 (s, phosphate). – MS (MALDI, negative mode, matrix: ATT): *m/z*: 701 $[M - NHEt_3]^-$, 803.76 for $C_{33}H_{50}N_5O_{16}P$.

Phosphate 2: To a solution of the triethylammonium salt of compound **38** (37 mg, 0.046 mmol) in dry methanol (3 mL) was added a solution of sodium methoxide in dry methanol (0.5 M, 0.3 mL). After 1 h the solution was neutralised with Amberlite IRC 176 (H^+) and evaporated. The residue was dissolved in methanol/water (1:1, 3 mL), and NaOH (1 M, 0.5 mL) was added. After stirring overnight the solution was neutralised with IRC 176 (H^+), the pH value was adjusted to 8 with NaOH, and the solvents were removed by lyophilisation. The residue was purified by precipitation from water with ethanol and acetone to afford the disodium salt **2** (18 mg, 69%) as a colourless powder. – TLC (ethyl acetate/methanol/1 M $NH_4CH_3CO_2$ 1:1:1): R_f = 0.56, $[\alpha]_D$ = 33.0 (*c* = 0.5, H_2O). – ^{1}H NMR (600 MHz, D_2O): δ = 1.91 (s, 3 H, N-Ac), 1.94 (ddd, $J_{6a'',6b''}$ = 13.8 Hz, $J_{6a'',5''}$ = 10.4 Hz, *J* = 3.2 Hz, 1 H, 6a′′-H), 2.13 (dd, $J_{6b',6a''}$ = 13.8 Hz, $J_{6b'',5''}$ = 3.3 Hz, 1 H, 6b′′-H), 3.98–4.01 (m 1 H, 5a′-H), 4.05–4.09 (m, 1 H, 5b′-H), 4.10–4.15 (m, 2 H, 4′-, 5′′-H), 4.17–4.22 (m, 2 H, 2′-, 3′-H), 4.47 (dd, $J_{4'',5''} \approx J_{4'',3''} \approx$ 4.4 Hz, 1 H, 4′′-H), 5.71 (dd, $J_{3'',2''}$ = 10 Hz, $J_{3'',4''}$ = 4.6 Hz, 1 H, 3′′-H), 5.88 (d, $J_{1',2'}$ = 4.0 Hz, 1 H, 1′-H), 6.01 (d, $J_{5,6}$ = 7.6 Hz, 1 H, 5-H), 6.09 (d, $J_{2'',3''}$ = 10.0 Hz, 1 H, 2′′-H), 7.85 (d, $J_{6,5}$ = 7.6 Hz, 1 H, 6-H). – ^{13}C NMR (150.9 MHz, D_2O): δ = 23.37 (Ac–CH_3), 38.14 (d, $^3J_{P,C}$ = 7 Hz, 6′′-C), 48.86 (4′′-C), 65.35 (d, $^2J_{P,C}$ = 5.8 Hz, 5′-C), 66.53 (5′′-C), 70.66 (3′-C), 75.56 (2′′-C), 80.70 (d, $^2J_{P,C}$ = 7.5 Hz, 1′′-C), 81.10 (d, $_3J_{P,C}$ = 8.7 Hz, 4′-C) 90.53 (1′-C), 97.80 (5-C), 129.94 (3′′-C), 131.62 (2′′-C), 142.77 (6-C), 159.11 (4-C), 167.54 (2-C), 175.54 (C=O). – ^{31}P NMR (161.7 MHz, D_2O): d = –2.91 (s, phosphate). – MS (FAB, negative mode, H_2O/glycerol): *m/z*: 519 $[M - 2\ Na + H]^-$, 541 $[M - Na]^-$, 563 $[M - H]^-$, 564.08 for $C_{18}H_{23}N_4Na_2O_{12}P$.

Methyl (3*S*,4*R*,5*R*)-4,5-*O*-Cyclohexylidene-3,4,5-trihydroxycyclohex-1-ene-1-carboxylate (40): Compound **40** was prepared according to a procedure by Shing et al.[14]

Methyl (3*R*,4*R*,5*R*)-3-*O*-Benzoyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxycyclohex-1-ene-1-carboxylate (41): The alcohol **40** (10 g, 37.37 mmol), benzoic acid (8.64 g, 70.81 mmol), and triphenylphosphane (18.6 g, 70.81 mmol) were dried overnight in a desiccator. The mixture was dissolved in dry THF (200 mL) and diisopropyl azodicarboxylate (14.3 g, 70.81 mmol) in dry THF (10 mL) was added slowly. After the lightly exothermic reaction was finished, the solution was stirred for 2 h at room temp. and then evaporated. The residue was purified by flash chromatography (1. toluene/ethyl acetate 50:1 and 2. petroleum ether ether/ethyl acetate 9:1) to afford the benzoate **41** (13 g, 94%) as a colourless solid. m.p. 91–92 °C, TLC (toluene/ethyl acetate, 6:1): R_f = 0.61, $[\alpha]_D$ = –107.4 (*c* = 1, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30–1.70 (m, 10 H, cyclohexylidene), 2.57–2.68 (m, 1 H, 6a-H), 2.94 (dd, ^2J = 17.2 Hz, $J_{6b,5}$ = 6.0 Hz, 1 H, 6b-H), 3.74 (s, 3 H, COOMe), 4.39 (dd, $J_{4,5}$ = 6.7 Hz, $J_{4,3}$ = 4.7 Hz, 1 H, 4-H), 4.53 (ddd, $J_{5,4} \approx J_{5,6b} \approx$ 6.4 Hz, $J_{5,6a}$ = 4.2 Hz, 5-H), 5.58–5.60 (m, 1 H, 3-H), 6.96–6.99 (m, 1 H, 2-H), 7.38–7.45 (m, 2 H, Ph), 7.52–7.60 (m, 1 H, Ph), 8.00–8.05 (m, 2 H, Ph). – $C_{21}H_{24}O_6$ (372.4) calcd.: C 67.73, H 6.50; found: C 67.97, H 6.45.

Methyl (3*R*,4*R*,5*R*)-3-*O*-Benzoyl-3,4,5-trihydroxycyclohex-1-ene-1-carboxylate (42): Compound **41** (12.7 g, 34 mmol) was dissolved in acetic acid (90%, 150 mL) and stirred 3 h at 60–70 °C. The acetic acid was removed under vacuum, and the residue was twice coevaporated with ethanol. The resulting yellow oil was purified by flash chromatography (toluene/acetone, 4:1) to yield the diol **42** (9.32 g, 94%) as a colourless oil which solidifies on standing. m.p. 84–85 °C, TLC (toluene/acetone, 4:1): R_f = 0.2, $[\alpha]_D$ = –118.3 (*c* = 2, $CHCl_3$) – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.54–2.75 (m, 2 H, 6a,b-H), 2.90 (br. s, 2 H, OH), 3.74 (s, 3 H, COOMe), 3.96 (dd,

$J_{4,3}$ = 7.0 Hz, $J_{4,5}$ = 2.5 Hz, 1 H, 4-H), 4.24 (ddd, $J_{5,6a} \approx J_{5,6b} \approx$ 4.0 Hz, $J_{5,4}$ = 2.5 Hz,1 H, 5-H), 5.75–5.82 (m, 1 H, 3-H), 6.78–6.81 (m, 1 H, 2-H), 7.39–7.45 (m, 2 H, Ph), 7.52–7.60 (m, 1 H, Ph), 8.00–8.05 (m, 2 H, Ph). – $C_{15}H_{16}O_6$ (292.3) calcd.: C 61.64, H 5.5; found: C 61.95, H 5.49.

(3*R*,4*R*,5*R*)-3,4,5-Tri-*O*-acetyl-3,4,5-trihydroxycyclohex-1-ene-1-carboxylate (43): To a solution of diol **42** (1.73 g, 5.93 mmol) in methanol (50 mL) was added NaOH (1 M, 5 mL). After 2 d stirring a room temp. the solution was neutralised and converted into the free acid with Amberlite IR 120 (H^+). The solvents were evaporated and the residue was dissolved in pyridine/acetic anhydride (2:1, 15 mL). After 5 h stirring the solution was concentrated under vacuum, the residue was dissolved in ethyl acetate and washed twice with HCl (1 M) and brine. The organic phase was dried with $MgSO_4$, evaporated, and the residue purified by flash chromatography (toluene/acetone, 8:1 + 0.5% AcOH) to afford the free acid **43** (1.47 g, 83%) as a colourless, gluey foam. – TLC (toluene/acetone, 6:1+ 0.5% AcOH): R_f = 0.31, $[\alpha]_D$ = –155.0 (c = 1.25, CH_2Cl_2). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.03/2.05/2.08 (3 s, 9 H, 3 Ac), 2.53–2.77 (m, 2 H, 6a,b-H), 5.13 (dd, $J_{4,3}$ = 7.4 Hz, $J_{4,5}$ = 2.4 Hz, 1 H, 4-H), 5.41 (ddd, $J_{5,6a} \approx J_{5,6b} \approx$ 4.4 Hz, $J_{5,4}$ = 2.4 Hz, 1 H, 5-H), 5.63–5.68 (m, 1 H, 3-H), 6.82–6.84 (m, 1 H, 2-H), 9.65 (br. s, 1 H, COOH). – $C_{13}H_{16}O_8$ (300.3) calcd.: C 52.00, H 5.37; found: C 52.61, H 5.78.

(3*R*,4*R*,5*R*)-3,4,5-Tri-*O*-acetyl-3,4,5-trihydroxy-*N*-methoxy-*N*-methylcyclohex-1-ene-1-carboxamide (44): The solution of acid **43** (300 mg, 0.99 mmol) in dry dichloromethane (20 mL) was cooled to –20 °C. *N*-methylpiperidine (140 μL, 1.15 mmol) was added, and then ethyl chloroformate (106 μL, 1.1 mmol) was dropped in slowly. After 10 min stirring at –20 °C a solution of *N,O*-dimethylhydroxylamine hydrochloride (107 mg, 1.1 mmol) and *N*-methylpiperidine (140 μL, 1.15 mmol) in dry dichloromethane (15 mL) was dropped in slowly and stirred for 1 h. After warming to room temp. the solution was stirred for 2 h and then was again cooled to –20 °C. *N*-methylpiperidine (64 μL, 0.52 mmol) followed by ethyl chloroformate (64 μL, 0.5 mmol) were added slowly. After 10 min a solution of *N,O*-dimethylhydroxylamine hydrochloride (49 mg, 0.5 mmol) and *N*-methylpiperidine (64 μL, 0.52 mmol) in dry dichloromethane (5 mL) was added, and the solution was stirred for 30 min at –20 °C. After warming to room temp. the solution was stirred until total conversion of the starting material. Water was then added, the phases were separated, and the organic phase washed twice with HCl (0.1 M) and once with sodium bicarbonate. The organic phases were dried with $MgSO_4$, evaporated, and the residue was purified by flash chromatography (toluene/acetone, 6:1) to afford the Weinreb amide **44** (250 mg, 73%) as colourless oil. – TLC (toluene/acetone, 6:1): R_f = 0.16, $[\alpha]_D$ = –115.0 (c = 2, CH_2Cl_2). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.03/2.04/2.05 (3 s, 9 H, 3 Ac), 2.52–2.63 (m, 1 H, 6a-H), 2.71–2.82 (m, 1 H, 6b-H), 3.20 (s, 3 H, NMe), 3.62 (s, 3 H, OMe), 5.15 (dd, $J_{4,3}$ = 6.9 Hz, $J_{4,5}$ = 2.4 Hz, 1 H, 4-H), 5.39 (ddd, $J_{5,6a} \approx J_{5,6b} \approx$ 4.8 Hz, $J_{5,4}$ = 2.4 Hz, 1 H, 5-H), 5.53–5.60 (m, 1 H, 3-H), 6.01–6.05 (m, 1 H, 2-H). – $C_{15}H_{21}NO_8$ (343.3) calcd.: C 52.48, H 6.16, N 4.08; found: C 52.98, H 6.51, N 3.89.

(3*R*,4*R*,5*R*)-3,4,5-Tri-*O*-acetyl-3,4,5-trihydroxycyclohex-1-ene-1-carbaldehyde (45): To a solution of amide **44** (90 mg, 0.26 mmol) in dry toluene (10 mL) and dry THF (4 mL) was added RedAl at –60 °C (0.12 mL, 0.39 mmol, 3.4 M in toluene) under an argon atmosphere. After 30 min at –60 °C the reaction was quenched with potassium sodium tartrate (15 mL) and warmed to room temp. The phases were separated and the aqueous phase was extracted once with ethyl acetate. The combined organic phases were washed with HCl (1 M), sodium bicarbonate, and brine. After drying with $MgSO_4$ the solvents were removed under vacuum and the residue was purified by flash chromatography (toluene/acetone, 6:1) to yield the aldehyde **45** (33 mg, 45%) [besides some re-isolated starting material (23 mg, 25%)]. m.p. 93–94 °C, TLC (toluene/acetone, 4:1): R_f = 0.55, $[\alpha]_D$ = –76.5 (c = 1, CH_2Cl_2). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.03/2.04/2.10 (3 s, 9 H, 3 Ac), 2.50–2.70 (m, 2 H, 6a,b-H), 5.17 (dd, $J_{4,3}$ = 7.3 Hz, $J_{4,5}$ = 2.4 Hz, 1 H, 4-H), 5.43 (ddd, $J_{5,6a} \approx J_{5,6b} \approx$ 4.5 Hz, $J_{5,4}$ = 2.4 Hz, 1 H, 5-H), 5.68–5.74 (m, 1 H, 3-H), 6.58–6.61 (m, 1 H, 2-H), 9.51 (s, 1 H, CHO). – $C_{13}H_{16}O_7$ (284.3) calcd.: C 54.93, H 5.67; found: C 54.97, H 5.66.

Phosphonate (*S*)-46: To a solution of aldehyde **45** (120 mg, 0.42 mmol) in dry dichloromethane (3 mL) was added diallyl phosphite[24] (89 mg, 0.55 mmol) and triethylamine (18 μL, 0.13 mmol). After stirring overnight the solvent was evaporated and the residue was purified by flash chromatography to afford the hydroxyphosphonate (170 mg, 91%) as a colourless oil. The two diastereoisomers could be separated by repeating MPLC (toluene/ethyl acetate 1:7), whereas pure (*R*)-**46** was first eluted followed by (*S*)-**46** which was obtained in 90% purity.

(*R*)-46: TLC (toluene/acetone, 2:1): R_f = 0.19, $[\alpha]_D$ = –107 (c = 0.5, CH_2Cl_2). – ^{1}H NMR (250 MHz, [D$_4$]methanol): δ = 2.02/2.03/2.06 (3 s, 9 H, 3 Ac), 2.45–2.55 (m, 1 H, 6a-H), 2.65–2.80 (m, 1 H, 6b-H), 4.53 (d, $J_{1',P}$ = 14.7 Hz, 1 H, 1′-H), 4.57–4.65 (m, 4 H, 2 CH_2CH=CH$_2$), 5.16 (dd, $J_{4,3}$ = 6.4 Hz, $J_{4,5}$ = 2.4 Hz, 1 H, 4-H), 5.21–5.36 (m, 4 H, 2 CH$_2$CH=CH_2), 5.40–5.50 (m, 2 H, 3-, 5-H), 5.81–5.89 (m, 1 H, 2-H), 5.90–6.07 (m, 2 H, 2 CH$_2$CH=CH$_2$). – ^{31}P NMR (161.7 MHz, [D$_4$]methanol): δ = 22.22 (s, phosphonate).

(*S*)-46: TLC (toluene/acetone, 2:1): R_f = 0.19, $[\alpha]_D$ = –117.2 (c = 0.5, CH_2Cl_2). – ^{1}H NMR (250 MHz, [D$_4$]methanol): δ = 2.03/2.04/2.05 (3 s, 9 H, 3 Ac), 2.50–2.70 (m, 2 H, 6a,b-H), 4.50 (d, $J_{1',P}$ = 15.0 Hz, 1 H, 1′-H), 4.53–4.66 (m, 4 H, 2 CH_2CH=CH$_2$), 5.14 (dd, $J_{4,3}$ = 6.6 Hz, $J_{4,5}$ = 2.4 Hz, 1 H, 4-H), 5.20–5.36 (m, 4 H, 2 CH$_2$CH=CH_2), 5.39–5.42 (m, 1 H, 5-H), 5.43–5.57 (m, 1 H, 3-H), 5.80–5.88 (m, 1 H, 2-H), 5.90–6.06 (m, 2 H, 2 CH$_2$CH=CH$_2$). – ^{31}P NMR (161.7 MHz, [D$_4$]methanol): δ = 22.14 (s, phosphonate). For the mass spectra and the elemental analysis a mixture of the diastereoisomers was used: MS (MALDI, positive mode, matrix: DHB): m/z: 470 [M + Na]$^+$, $C_{19}H_{27}O_{10}P$ (446.4) calcd.: C 51.12, H 6.10; found: C 51.20, H 6.26.

Phosphate (*R*)-48: Compound (*R*)-**46** (30 mg, 67 μmol) and cytidine phosphitamide **47** (46 mg, 81 μmol) were coevaporated with dry dichloromethane and dried under high vacuum. The mixture was dissolved in a small amount of dry dichloromethane, and tetrazole (7 mg, 100 μmol) was added. After 3 h stirring at room temp. the coupling reaction was complete and *t*BuOOH (25 μL, 134 μmol 5.5 M in nonane) was added. After 1 h triethylamine (1 mL) was added, and the solution stirred overnight. Evaporation of the solvents and purification by flash chromatography (ethyl acetate/methanol 5:1 + 1% NEt$_3$) afforded the triethylammonium salt (*R*)-**48** (60 mg, 91%) as a colourless lyophilisate. – TLC (ethyl acetate/methanol 3:1 + 1% NEt$_3$): R_f = 0.18, $[\alpha]_D$ = –12.6 (c = 0.5, methanol). – ^{1}H NMR (250 MHz, [D$_4$]methanol): δ = 1.30 (t, J = 7.3 Hz, 9 H, NCH$_2$CH_3), 2.00/2.01/2.02/2.07/2.09/2.17 (6 s, 18 H, 6 Ac), 2.58–2.88 (m, 2 H, 6a,b′′-H), 3.20 (q, J = 7.3 Hz, 6 H, NCH_2CH$_3$), 4.08–4.27 (m, 2 H, 5a,b′-H), 4.38–4.41 (m, 1 H, 4′-H), 4.60–4.71 (m, 4 H, 2 CH_2CH=CH$_2$), 5.08 (dd, $^2J_{1''',P}$ = 15.4 Hz, $^3J_{1''',P}$ = 10.7 Hz, 1 H, 1′′′-H), 5.17 (dd, $J_{4'',3''}$ = 6.7 Hz, $J_{4'',5''}$ = 2.4 Hz, 1 H, 4′′-H), 5.21–5.53 (m, 8 H, 2′-,3′-,3′′,-5′′-H, 2 CH$_2$CH=CH_2), 5.80–5.90 (m, 1 H, 2′′-H), 5.91–6.07 (m, 2 H, 2

$CH_2CH{=}CH_2$), 6.19 (d, $J_{1',2'}$ = 4.1 Hz, 1 H, 1′-H), 7.53 (d, $J_{5,6}$ = 7.6 Hz, 1 H, 5-H), 8.42 (d, $J_{6,5}$ = 7.6 Hz, 1 H, 6-H). – ^{31}P NMR (161.7 MHz, [D$_4$]methanol): δ = –0.60 (d, $J_{P,P}$ = 33.4 Hz, phosphate), 19.25 (d, $J_{P,P}$ = 33.4 Hz, phosphonate). – MS (MALDI, negative mode, matrix: ATT): *m*/*z*: 837 [M – NHEt$_3$–Allyl+H]$^-$, 877 [M – NHEt$_3$]$^-$. – $C_{40}H_{60}N_4O_{20}P_2 \cdot 1.5\ H_2O$ (978.9) calcd.: C 47.77, H 6.31, N 5.57; found: C 47.83, H 6.64, N 5.23.

Phosphate (*S*)-48: As described for compound (*R*)-**48**, the hydroxyphosphonate (*S*)-**46** (47 mg, 0.105 mmol) was coupled with cytidine phosphitamide **47** (72 mg, 0.126 mmol) by tetrazole activation (11 mg, 0.138 mmol). After oxidation with *t*BuOOH (38 μL, 0.21 mmol 5.5 M in nonane) and deprotection of the cyanoethyl group with triethylamine, (*S*)-**48** (89 mg, 87%) was obtained as a colourless lyophilisate. – TLC (ethyl acetate/methanol 3:1 + 1% NEt$_3$): R_f = 0.18, [α]$_D$ = –36.1 (*c* = 0.96, methanol). – ^{1}H NMR (250 MHz, [D$_4$]methanol): δ = 1.31 (t, *J* = 7.3 Hz, 9 H, NCH_2CH_3), 2.01/2.03/2.06/2.11/2.17 (5 s, 18 H, 6 Ac), 2.60–2.80 (m, 2 H, 6a,b′′-H), 3.20 (q, *J* = 7.3 Hz, 6 H, NCH_2CH_3), 4.08 (ddd, ^2J = 11.6 Hz, $J_{5a',P}$ = 4.5 Hz, $J_{5a',4'}$ = 2.7 Hz, 1 H, 5a′-H), 4.23 (ddd, ^2J = 11.6 Hz, $J_{5b',P}$ = 5.0 Hz, $J_{5b',4'}$ = 2.5 Hz, 1 H, 5b′-H), 4.36–4.40 (m, 1 H, 4′-H), 4.62–4.70 (m, 4 H, 2 $CH_2CH{=}CH_2$), 5.01 (dd, $^2J_{1''',P}$ = 15.0 Hz, $^3J_{1''',P}$ = 11.2 Hz, 1 H, 1′′′-H), 5.14 (dd, $J_{4'',3''}$ = 7.0 Hz, $J_{4'',5''}$ = 2.4 Hz, 1 H, 4′′-H), 5.21–5.60 (m, 8 H, 2′-,3′-,3′′,-5′′-H, 2 $CH_2CH{=}CH_2$), 5.90–6.06 (m, 3 H, 2′′-H, 2 $CH_2CH{=}CH_2$), 6.22 (d, $J_{1',2'}$ = 4.8 Hz, 1 H, 1′-H), 7.52 (d, $J_{5,6}$ = 7.6 Hz, 1 H, 5-H), 8.41 (d, $J_{6,5}$ = 7.6 Hz, 1 H, 6-H). – ^{31}P NMR (161.7 MHz, [D$_4$]methanol): δ = –0.90 (d, $J_{P,P}$ = 30 Hz, phosphate), 19.08 (d, $J_{P,P}$ = 30 Hz, phosphonate). MS (MALDI, negative mode, matrix: ATT): *m*/*z*: 837 [M – NHEt$_3$ – Allyl + H]$^-$, 877 [M – NHEt$_3$]$^-$, 978.9 for $C_{40}H_{60}N_4O_{20}P_2$.

Phosphate (*R*)-3: To a solution of compound (*R*)-**48** (40 mg, 41 μmol) and dimedone (57 mg, 419 μmol) in dry THF (1 mL) was added Pd(PPh$_3$)$_4$ (5 mg, 4.1 μmol) in the dark. In the next 4 h, Pd(PPh$_3$)$_4$ (5 mg) was added twice, then triethylamine was added and the solvent removed under vacuum. The dimedone was removed by RP-18 chromatography (ethanol/water, 1:3) and the residue was dissolved in aqueous ammonia (25%, 3 mL) and stirred overnight. The solution was evaporated under vacuum and the residue was converted into the sodium salt with Amberlite IR 120 (Na$^+$) and lyophilised from water. The residue was purified by precipitation form water with ethanol/acetone to yield the pure trisodium salt (*R*)-**3** (22 mg, 88%) as a colourless powder. – TLC (ethyl acetate/methanol/1 M $CH_3CO_2NH_4$ 1:1:0.5): R_f = 0.1, [α]$_D$ = 13.2 (*c* = 1, H$_2$O). – ^{1}H NMR (250 MHz, D$_2$O): δ = 2.14–2.25 (m, 1 H, 6a′′-H), 2.42–2.53 (m, 1 H, 6b′′-H), 3.54 (dd, $J_{4'',3''}$ = 5.5 Hz, $J_{4'',5''}$ = 2.4 Hz, 1 H 4′′-H), 3.82–3.91 (m, 1 H, 5′′-H), 4.00–4.10 (m, 5 H, 2′-,4′-,5a,b′-,3′′-H), 4.12–4.20 (m, 1 H, 3′-H), 4.27 (dd, $J_{1''',P}$ = 13.8 Hz, $J_{1''',P}$ = 9.7 Hz, 1 H, 1′′′-H), 5.50 (m, 1 H, 2′′-H), 5.75 (d $J_{1',2'}$ = 3.0 Hz, 1 H, 1′-H), 5.93 (d, $J_{5,6}$ = 7.5 Hz, 1 H, 5-H), 7.83 (d, $J_{6,5}$ = 7.5 Hz, 1 H, 6-H). – ^{13}C NMR (150.9 MHz, D$_2$O): d = 31.45 (6′′-C), 64.47 (d, $^2J_{5',P}$ = 4.6 Hz, 5′-C), 68.59 (5′′-C), 69.19 (3′-C), 70.43 (3′′-C), 74.64 (4′′-C), 75.51 (2′′-C), 79.03 (dd, $^1J_{1''',P}$ = 149.7 Hz, $^2J_{1''',P}$ = 8.7 Hz, 1′′′-C), 83.35 (d, $^3J_{4''',P}$ = 8.7 Hz, 4′-C), 90.68 (1′-C), 97.35 (5-C), 123.22 (d, $^3J_{2''',P}$ = 8.1 Hz, 2′′-C), 138.07 (1′′-C), 142.37 (6-C), 158.61 (4-C), 167.19 (2-C). – ^{31}P NMR (161.7 MHz, D$_2$O): δ = 1.22 (d, $J_{P,P}$ = 31 Hz, phosphate), 12.71 (d, $J_{P,P}$ = 31 Hz, phosphonate). – MS (MALDI, negative mode, matrix: ATT): *m*/*z*: 544 [M – 3 Na + 2 H]$^-$, 567 [M – 2 Na + 1 H]$^-$, 611.0 for $C_{16}H_{22}N_3Na_3O_{14}P_2$.

Phosphate (*S*)-3: As described for (*R*)-**3** compound, (*S*)-**48** was converted into the trisodium salt (*S*)-**3** (22 mg, 88%), contaminated with 4% (*R*)-**3**. – TLC (ethyl acetate/methanol/1 M $CH_3CO_2NH_4$, 1:1:0.5): R_f = 0.1, [α]$_D$ = –28.4 (*c* = 0.66, H$_2$O). – ^{1}H NMR (250 MHz, D$_2$O): δ = 2.18–2.32 (m, 1 H, 6a′′-H), 2.33–2.48 (m, 1 H, 6b′′-H), 3.54 (dd, $J_{4'',3''}$ = 6.1 Hz, $J_{4'',5''}$ = 2.4 Hz, 1 H 4′′-H), 3.88–4.17 (m, 7 H, 2′-,3′-,4′-,5a,b′-,3′′-,5′′-H), 4.38 (dd, $J_{1''',P}$ = 14.3 Hz, $J_{1''',P}$ = 9.7 Hz, 1 H, 1′′′-H), 5.54 (m, 1 H, 2′′-H), 5.78 (d $J_{1',2'}$ = 4.0 Hz, 1 H, 1′-H), 5.92 (d, $J_{5,6}$ = 7.6 Hz, 1 H, 5-H), 7.77 (d, $J_{6,5}$ = 7.6 Hz, 1 H, 6-H). – ^{31}P NMR (161.7 MHz, D$_2$O): δ = 1.02 (d, $J_{P,P}$ = 31 Hz, phosphate), 13.55 (d, $J_{P,P}$ = 31 Hz, phosphonate). – MS (MALDI, negative mode, matrix: ATT): *m*/*z*: 545 [M – 3 Na + 2 H]$^-$, 611.0 for $C_{16}H_{22}N_3Na_3O_{14}P_2$.

Phosphate (*E*)-4: To a solution of compound (*R,S*)-**48** (100 mg, 0.1 mmol) in dry THF (3 mL) was added DBU (90 μL, 0.6 mmol) and the solution was heated to 60–70 °C overnight. After cooling to room temp. pyridine/acetic anhydride (1.5:1, 1.5 mL) and dry THF (3 mL) were added and the solution was stirred for 3 h. The solvents were removed under vacuum and residue was purified by flash chromatography (ethyl acetate/methanol, 6:1 + 1% NEt$_3$ → 2:1 + 1% NEt$_3$) to yield the eliminated compound (90 mg) contaminated with large amounts of acetate as a brown oil (R_f = 0.2 (ethyl acetate/methanol, 1:1 + 1% NEt$_3$), MS (MALDI, negative mode, matrix: ATT): *m*/*z*: 776 [M – NHEt$_3$ – Allyl]$^-$, 835 [M – NHEt$_3$ + H$_2$O]$^-$, 918.31 for $C_{38}H_{56}N_4O_{18}P_2$). Half of the brown oil (≈ 45 mg) and dimedone (70 mg, 0.5 mmol) were dissolved in dry THF (2 mL) and Pd(PPh$_3$)$_4$ (6 mg, 0.005 mmol) added in the dark. During the next 6 h, Pd(PPh$_3$)$_4$ (5 mg) was added twice and the solution was stirred overnight in the dark. Triethylamine was added and the solvent was removed under vacuum. The dimedone was separated by RP-18 chromatography (ethanol/water 1:3) and the residue was dissolved in aqueous ammonia (25%, 3 mL). After stirring overnight the solution was evaporated and the residue was purified by preparative HPLC (0.05 M TEAB + 0.5% CH_3CN, flow: 10 mL/min). The compound was converted into the sodium salt by IR 120 (Na$^+$) and lyophilised to yield the trisodium salt (*E*)-**4** (10 mg, 34%) as a colourless powder. – HPLC (präp RP18, 0.05 M TEAB + 0.5% CH_3CN, 10 mL/min): t_R = 18.9 min. – ^{1}H NMR (250 MHz, D$_2$O): δ = 2.64–2.68 (m, 2 H, 6a,b′′-H), 3.74–3.82 (m, 1 H, 5′′-H), 4.03–4.19 (m, 6 H, 2′-,3′-,4′-,5a,b′-,4′′-H), 5.60–5.70 (m, 1 H, 3′′-H), 5.75 (d, $J_{1',2'}$ = 3.7 Hz, 1 H, 1′-H), 5.91 (d, $J_{5,6}$ = 7.6 Hz, 1 H, 5-H), 6.56 (d, $J_{2'',3''}$ = 10.1 Hz, 1 H, 2′′-H), 7.77 (d, $J_{6,5}$ = 7.6 Hz, 1 H, 6-H). – ^{13}C NMR (150.9 MHz, D$_2$O): δ = 29.97 (6′′-C), 65.54 (5′-C), 67.61 (4′′-C), 68.85 (5′′-C), 69.58 (3′-C), 75.38 (2′-C), 83.51 (d, $J_{4',P}$ = 8.7 Hz, 4′-C), 90.47 (1′-C), 97.39 (5-C), 126.68 (d, $J_{2'',P}$ = 11 Hz, 2′′-C), 130.52 (3′′-C), 142.41 (6-C), 158.66 (4-C), 167.18 (2-C). – ^{31}P NMR (243 MHz, D$_2$O): δ = –5.09 (br. s, phosphate), 2.69 (br. s, phosphonate). – MS (MALDI, negative mode, matrix: ATT): *m*/*z*: 527 [M – 3 Na + 2 H]$^-$, 570 [M – Na]$^-$, 592 [M – H]$^-$, 593.01 for $C_{16}H_{20}N_3Na_3O_{13}P_2$.

Phosphonate (*R,S*)-50: To a solution of (*R*)-**46** (15 mg, 33.6 mmol) in dry pyridine (1 mL) was added, at 0 °C, (*R*)-**49**[24] (13 mL, 67 mmol). After 2 h stirring at room temp. the reaction mixture is concentrated in vacuo. Flash chromatography with toluene/acetone (6:1) as eluent gave (*R,S*)-50 (18 mg, 85%) as colorless oil. – TLC (toluene/acetone, 2:1): R_f = 0.53. – ^{1}H NMR (250 MHz, [D$_4$]MeOD): δ = 2.03/2.05 (2 s, 9 H, 3 Acetyl), 2.18–2.32 (m, 1 H, 6_a-H), 2.43–2.56 (m, 1 H, 6_b-H), 3.63 (d, $J_{OMe,F}$ = 1.2 Hz, 3 H, OMe), 4.55–4.68 (m, 4 H, 2 $CH_2CH{=}CH_2$), 5.08 (dd, $J_{4,3}$ = 6.4, $J_{4,5}$ = 2.3 Hz, 1 H, 4-H), 5.14–5.42 (m, 6 H, 3-, 5-H, 2 $CH_2CH{=}CH_2$), 5.64–5.72 (m, 1 H, 2-H), 5.87 (d, $J_{1',P}$ 13.4 Hz, 1 H, 1′-H), 5.86–6.02 (m, 2 H, 2 $CH_2CH{=}CH_2$), 7.43–7.53 (m, 5 H, Phenyl). – ^{31}P NMR (161.7 MHz, [D$_4$]MeOD): δ = 16.67 (s, phosphonate).

Phosphonate (*S,S*)-50: This compound was obtained from (*S*)-**46** and (*R*)-**49**[24] as described above. – TLC (toluene/acetone, 2:1)

R_f = 0.53. – ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.01/2.02/2.03 (3 s, 9 H, 3 Acetyl), 2.53–2.76 (m, 2 H, $6_{a,b}$-H), 3.48 (d, $J_{OMe,F}$ = 0.6 Hz, 3 H, OMe), 4.30–4.56 (m, 4 H, 2 CH_2CH=CH_2), 5.12 (dd, $J_{4,3}$ = 7.1 Hz, $J_{4,5}$ = 2.4 Hz, 1 H, 4-H), 5.17–5.33 (m, 2 H, 2 CH_2CH=CH_2), 5.38 (ddd, $J_{5,6a} \approx J_{5,6b} \approx 4.4$, $J_{5,4}$ = 2.4 Hz, 1 H, 5-H), 5.52–5.60 (m, 1 H, 3-H), 5.69–5.91 (m, 3 H, 2-H, 2 CH_2CH=CH_2), 5.73 (d, $J_{1',P}$ = 14 Hz, 1 H, 1′-H), 7.33–7.52 (m, 5 H, phenyl). – ^{31}P NMR (161.7 MHz, [D_4]MeOD): δ = 16.19 (s, phosphonate).

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