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Synthesis and antibacterial activity of mechanism-based inhibitors of KDO8P synthase and DAH7P synthase

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Abstract—KDO8PS (3-deoxy-D-*manno*-2-octulosonate-8-phosphate synthase) and DAH7PS (3-deoxy-D-*arabino*-2-heptulosonate-7-phosphate synthase) are attractive targets for the development of new anti-infectious agents. Both enzymes appear to proceed via a common mechanism involving the reaction of phosphoenolpyruvate (PEP) with arabinose 5-phosphate or erythrose-4-phosphate, to produce the corresponding ulosonic acids, KDO8P and DAH7P, respectively. The synthesis of new inhibitors closely related to the supposed tetrahedral intermediate substrates for the enzymes is described. The examination of the antibacterial activity of these derivatives is reported.
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Keywords: KDO8P synthase; DAH7P synthase; Lipopolysaccharide; Shikimate pathway; 2-Glycosyl-2-hydroxyphosphonopropanoic acid; Antibacterial activity

1. Introduction

3-Deoxy-D-*manno*-2-octulosonic acid 8-phosphate synthase (KDO8PS) and 3-deoxy-D-*arabino*-2-heptulosonic acid 7-phosphate synthase (DAH7PS) are important enzymes of bacterial metabolism. KDO8PS is a key enzyme in the biosynthesis of KDO, an essential sugar present in the lipopolysaccharide (LPS) of Gram-negative bacteria.[1] KDO acts as a linker between the inner core region and lipid A and is required for the biosynthesis of LPS. DAH7PS is the first enzyme in the shikimate pathway, which leads to the aromatic amino acids and other aromatic metabolites in microorganisms and plants.[2] The disruption of this pathway leads to rapid death of bacteria. Nevertheless DAH7PS has not been the target of anti-microbial research despite the fact that DAH7PS as KDO8PS are not known in mammalian physiology. As a result, the inhibition of these enzymes represents an attractive target for the development of new anti-infectious agents devoid of side effects.

The synthesis of new therapeutic agents directed against KDO8PS and DAH7PS requires detailed knowledge of the enzyme catalytic mechanism. Both enzymes, KDO8PS and DAH7PS appear to proceed by a common pathway[3] involving the condensation of phosphoenolpyruvate (PEP) with an aldose phosphate, arabinose 5-phosphate in the case of KDO8PS and erythrose-4-phosphate in the case of DAH7PS. These reactions produce two ulosonic acids, KDO-8-phosphate (KDO8P) and DAH-7-phosphate (DAH7P), respectively (Chart 1).

In the case of KDO8PS, it has been also established that the reaction mechanism implicates a cleavage of the C–O phosphate bond after an initial nucleophilic

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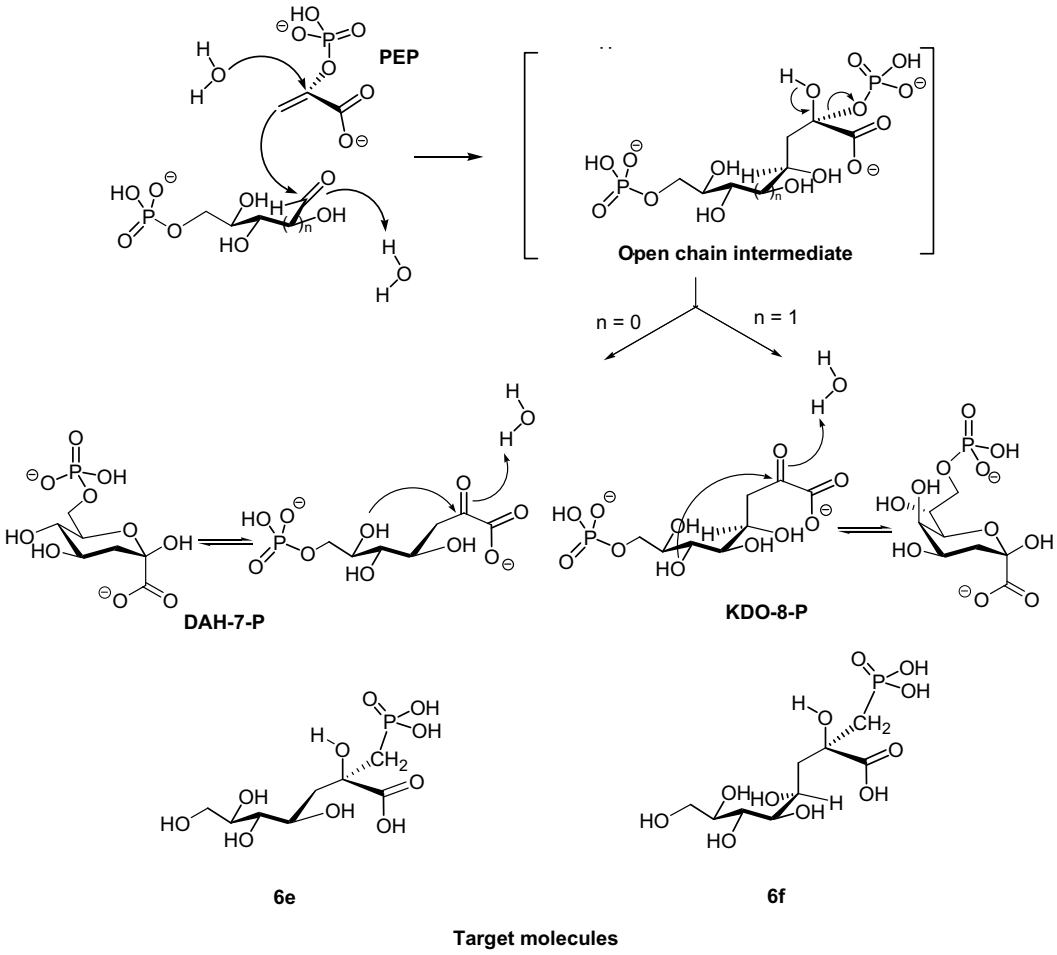


Chart 1. Proposed catalytic mechanism for KDO8PS and DAH7PS and the design of target molecules **6e**,**f**.

attack on the double bond of PEP, that involves a simultaneous reaction with aldehyde.[4] However, the detailed mechanism of KDO8PS is still debated. Two distinct pathways have been proposed, involving the formation of a cyclic[5] or open chain[6] intermediate. The data recently accumulated through syntheses and evaluations of reaction intermediates,[6a,c–e] crystallographic investigations[6b] and biochemical[6f–h] studies suggest that the reaction proceeds through the formation of the open chain intermediate. This proposal, coupled with our previous studies on the rational design of novel inhibitors of KDO8PS,[6b,7] lead us to consider the synthesis of new molecules that could exhibit structural and electronic properties closely related to the supposed open chain intermediate, and therefore can represent new antibacterial agents (Chart 1). For this purpose, we designed target molecules **6e** and **6f** where the C–O phosphate bond was replaced by a stable C–C link as the essential required modification relatively to the open chain intermediate and with a (*S*) configuration at C-4 in the case of **6f** for synthetic facilities. Phosphorylation at the primary alcohol was not attempted.

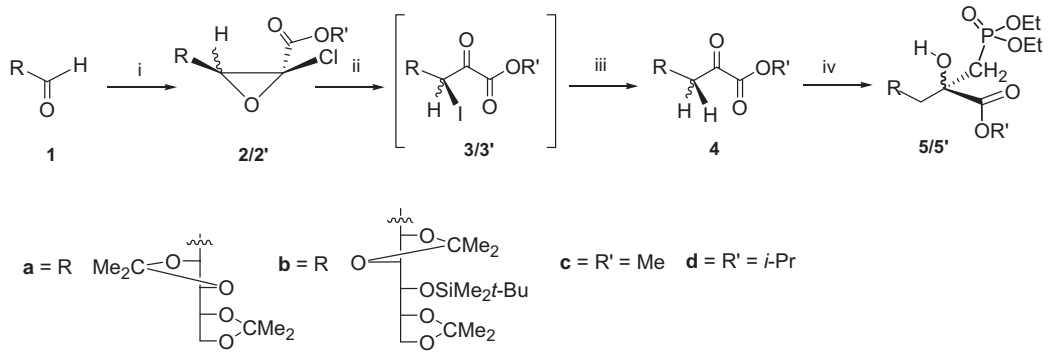
2. Results and discussion

2.1. Synthesis of target molecules 6

The proposed strategy to prepare the molecules **6e** and **6f** is based on the reaction between the lithiated carbanion derived from diethyl methylphosphonate and a suitable α-ketoacid derivative precursor.

The application of this strategy to the suitably protected aldose **1**, D-glucose or D-arabinose, led to the required glycosyl α-ketoester precursor **4**. Subsequent reaction between **4** and α-lithiated diethyl methylphosphonate gave the protected target molecules **5** (Scheme 1).

2.1.1. Preparation of α-ketoesters precursors 4. Glycosyl α-ketoesters **4** have already been prepared in two steps from the aldoses **1**.[8] Darzens reaction was performed with the potassium anion derived from alkyl dichloroacetate in alcohol–ether as solvent. Under these conditions, a diastereomeric mixture of α-chloroglycidic esters **2**/**2′** was obtained in high yields. Treatment of the



Scheme 1. Reagents and conditions: (i) $CHCl_2COOR'/Et_2O/R'OK/R'OH/0\ ^\circ C$; (ii) $MgI_2/Et_2O/35\ ^\circ C$; (iii) $NaHSO_3/H_2O$; (iv) $(EtO)_2P(O)CH_2Li$ (2 equiv)/THF/$-70\ ^\circ C$, HCl/Et_2O.

Table 1. Preparation of α-ketoesters precursors **4**

Starting substrate **1**	R′	**2**	Yield[a] (%)	**4**	Yield[a] (%)
1a	**c**	**2ac/2′ac**	94[c]	**4ac**	76
1a	**d**	**2ad/2′ad**	89 (65/35)[b]	**4ad**	86
1b	**c**	**2bc/2′bc**	81 (56/44)[b]	**4bc**	91
1b	**d**	**2bd/2′bd**	75 (60/40)[b]	**4bd**	92

[a] Yield of purified products.
[b] Diastereomeric ratios were evaluated by ^1H NMR (250 MHz) on the crude products.
[c] The nearest values of the NMR chemical shifts do not allow the evaluation of diastereomeric ratios.

mixture **2/2′** with magnesium iodide led to the rearrangement of the chloroepoxy ring into an epimeric mixture of non-isolated α-iodoketoesters **3/3′,** which was immediately treated with an aqueous solution of sodium hydrogen sulfite to yield the α-ketoesters **4** (Table 1).

2.1.2. Reaction of α-ketoesters 4 with diethyl α-lithiomethylphosphonate. Diethyl α-lithiomethylphosphonate is an useful reagent in organophosphorus chemistry allowing the preparation of numerous α-functionalized phosphonates by reaction with various electrophilic substrates.[9]

It is usually prepared by the addition of a solution of diethyl methylphosphonate in THF to *n*-butyllithium 1.6 M in hexane at $-70\ ^\circ C$.[10]

After 15 min, the α-ketoester **4** was added to the in situ generated carbanion at $-70\ ^\circ C$. The solution was stirred for 60 min at this temperature, then allowed to warm to $-35\ ^\circ C$ for 15 min, and was then treated with a saturated HCl ether solution at this temperature. Further hydrolysis at $-35\ ^\circ C$ and subsequent work-up afforded the α-hydroxy phosphonates **5/5′**.

Introduction order and quenching conditions were essential and required a careful control. An increase in temperature above $-35\ ^\circ C$, as well as a reverse introduction order of reagents favoured a partial Horner olefination with lithium diethylphosphate formation. In the case of **4bc**–**bd**, lithium diethylphosphate attacked the silylated ether to give diethyl *tert*-butyldimethylsilylphosphate as it can be observed by ^{31}P and ^1H NMR spectroscopy on the crude product (Scheme 2).

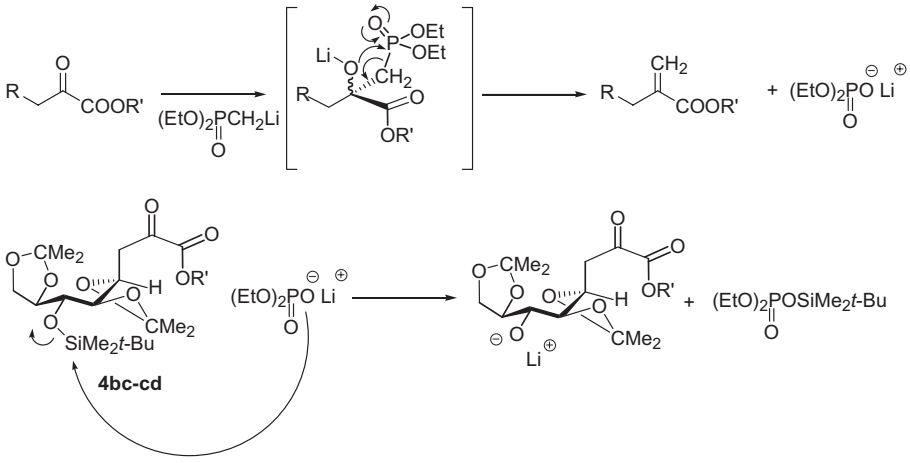
Addition of an HCl ether solution at low temperature before hydrolysis was necessary to avoid the olefination. Isopropyl and methyl carboxylic ester functions were stable and did not react with the lithiated carbanion.

Finally, under these conditions, the sole side reaction was the partial enolization of α-ketoesters **4** that resulted from the basicity of the starting reagent diethyl α-lithiomethylphosphonate. Purification of the crude product by chromatography over silica gel afforded a mixture of α-hydroxyphosphonate epimers **5/5′** in satisfactory yields (Table 2).

The epimer ratio was easily determined from the integration of signals in the ^{31}P NMR data. The obtained values clearly indicated that the reaction exhibited a low diastereoselectivity.

2.1.3. Deprotection of hydroxyphosphonates 5/5′. Deprotection of hydroxyphosphonates **5/5′** was the second key step of the synthesis of the target molecules **6e/6′e** and **6f/6′f**.

A study showed that the best conditions to obtain a total deprotection involved a two step sequence silylation/methanolysis. The silylation was carried out in 1,2-dichloroethane at 20 °C with an excess of bromotrimethylsilane (4 equiv) for 6 h. Further methanolysis for 15 h at 20 °C afforded completely deprotected 2-glycosyl-2-phosphonomethyl alcanoic acids **6** in quantitative yields (Scheme 3, Table 3).

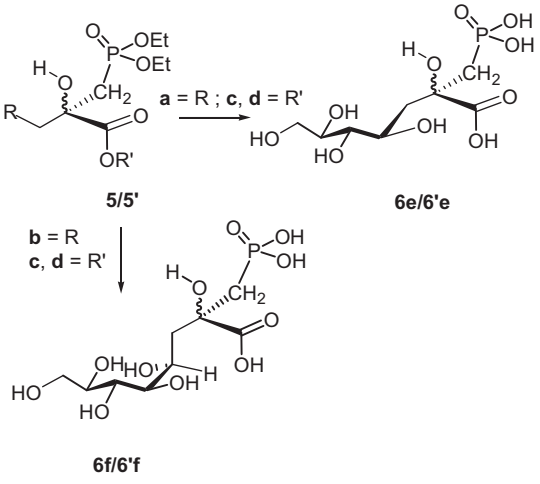


Scheme 2. Horner olefination of **4** and desilylation of **4bc**–**cd**.

Table 2. Reaction of α-ketoesters **4** with α-lithiomethylphosphonate

5/5′	Yield[a,b] (%)
5ac/5′ac	68 (61/39)
5ad/5′ad	68 (3/2)
5bc/5′bc	66 (51/49)
5bd/5′bd	62 (14/11)

[a] Yield of purified products.
[b] Diastereomeric ratio was evaluated by ^{31}P NMR on the crude products.



Scheme 3. Reagents and conditions: Me_3SiBr (4 equiv), 6 h, 20 °C, MeOH, 15 h, 20 °C.

With the purpose to carry out biological tests, it seemed also interesting to search for a modulation of the hydrophilic/hydrophobic balance in chemoselective deprotection of hydroxyphosphonates **5/5′** to favour their membrane transport. As a result, we studied the possible access either to alkyl alcanoates **7/7′** or diethylphosphono alcanoic acids **8/8′**. Selective removal of the diethyl phosphonic ester was reached with a tandem reaction silylation/hydrolysis at controlled pH to give **7/7′**.

The use of a large excess of triethylamine (13 equiv) during the silylation was a good solution in response to the sensitivity of the alcanoic ester moiety in **5/5′** towards Me_3SiBr/MeOH precedent procedure. Treatment of the resulting trimethylsilyl oxyphosphoryl moiety with wet ethylacetate cleanly led to the expected α-hydroxy phosphonic acid **7/7′** (Scheme 4i, Table 3).

It was worth of note that, under such conditions, the alcanoic ester as well as the dimethyl *tert*-butyl ether and diisopropylidene ketals were preserved.

After examining several inorganic and organic acids as releasing agents, we found that dry Amberlyst 15 in MeOH allowed the simultaneous removal of the isopropylidene and silylated groups of **7/7′** (Scheme 4ii, Table 3). Surprisingly, cleavage of the methyl and isopropyl carboxylic ester was also observed. Thus, the unusual liability of the carboxylic ester group and the simultaneous removal of the last protections afforded directly the target molecule **6/6′** in high yields. The ease with which the deprotection of these carboxylic esters occurred compared to that previously studied by us in the case of alkyl glycosyl phosphoenol pyruvate (other transition state analogues of KDO8PS) under similar reaction conditions has to be noted.[6d]

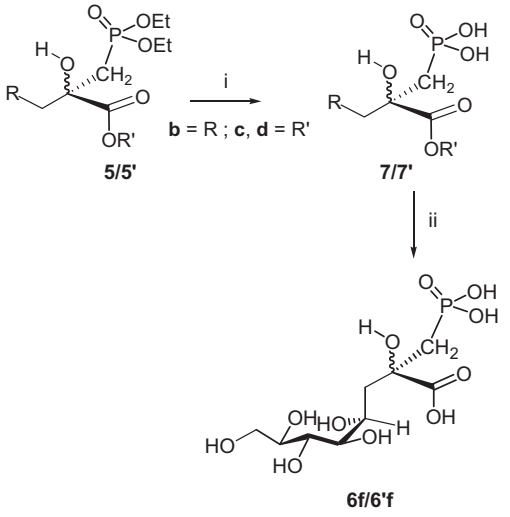
The overall reaction was extremely clean, the crude product was isolated without difficulty and was pure, as shown by the ^{31}P, ^{1}H and ^{13}C NMR spectra. As a consequence, this two steps sequence can be a possible alternative to the direct route described above to obtain **6/6′**. Conversely, it did not seem possible to release chemoselectively the hydroxyls and the phosphonic acid moiety without simultaneous deprotection of the carboxylic ester.

We have also studied a possible access to diethyl hydroxyphosphonates **8/8′** that needed other chemoselective deprotections. Contrarily to the precedent case, we found that the treatment of hydroxyphosphonates

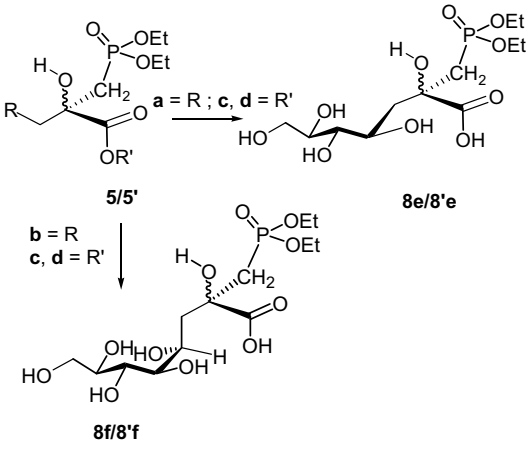
Table 3. Deprotection of hydroxyphosphonates **5/5′** into **6** or **7** or **8**

Starting substrate **5**	**6**	Yield[a,b] (%)	**7**	Yield[a,b] (%)	**8**	Yield[a,b] (%)
5ac/5′ac	**6e/6′e**	100 (52/48)[c] 97 (57/43)[d]			**8e/8′e**	100 (58/42)[d]
5ad/5′ad	**6e/6′e**	98 (3/2)[d]			**8e/8′e**	96 (56/44)[d]
5bc/5′bc	**6f/6′f**	100 (55/45)[c] 100 (3/2)[d]	**7bc/7′bc**	82 (72/28)[d]	**8f/8′f**	100 (53/47)[d]
5bd/5′bd	**6f/6′f**	98 (55/45)[c] 100 (53/47)[d]	**7bd/7′bd**	98 (80/20)[d]	**8f/8′f**	100 (53/47)[d]

[a] Yield of purified products.
[b] Diastereomeric ratios were evaluated by ^{31}P NMR on the crude products.
[c] Obtained from **7**.
[d] Obtained in one step from **5**.



Scheme 4. Reagents and conditions: (i) Me_3SiBr (5 equiv)/Et_3N (13 equiv), 18 h, 20 °C, then wet EtOAc; (ii) Amberlyst 15/MeCN 28 h, 20 °C.



Scheme 5. Reagents and conditions: Me_3SiBr (0.5 equiv)/MeOH, 15 h, 20 °C.

5/5′ with a solution of Me_3SiBr (0.5 equiv)/MeOH removed all the protecting groups except the diethyl phosphonic ester. Isopropylidene ketals, silylated ether and carboxylic ester moieties released the corresponding free hydroxyls under these conditions (Scheme 5, Table 3).

2.2. Antibacterial activity

Qualitative biological tests were carried out with compounds **6e/6′e**, **6f/6′f**, **8e/8′e** and **8f/8′f** on different Gram-negative bacteria, *Escherichia coli*, *Yersinia enterocolitica* and *Pseudomonas aeruginosa* and on two Gram-positive microorganisms, *Staphylococcus aureus* and *Bacillus subtilis*. The antibacterial activities were evaluated on Mueller–Hinton agar by using disk diffusion tests impregnated with 75 μg **6/6′** derivatives. The plates were incubated at 37 °C, with readings at 24 h of incubation.

All Gram-negative bacteria that possessed both enzymes KDO8PS and DAH7PS were affected by compounds **8e/8′e** and **8f/8′f** derived either from D-arabinose or D-glucose precursors, respectively. The largest zone inhibition was observed with *E. coli*. Antibacterial activity of compounds **6** was comparatively poor probably due to a low uptake through the bacterial outer membrane.

Only **8e/8′e** derived from D-arabinose precursor presented also a marked effect on Gram-positive bacteria, which are known to possess the DAHP7S and not the KDO8PS. Compounds **8f/8′f** derived from a D-glucose precursor was without effect on Gram-positive bacteria. As a consequence, we suppose that only **8e/8′e** was inhibitor of DAH7PS of Gram-positive and Gram-negative bacteria whereas **8f/8′f** could be a specific inhibitor of KDO8PS of the sole Gram-negative bacteria.

Further enzyme inhibition studies could confirm these first hypotheses.

3. Experimental

3.1. Reaction of α-ketoesters 4 with α-lithiomethylphosphonate

In a typical procedure, THF (8 mL) was added under N_2, at −30 °C, to *n*-BuLi 1.6 M in hexane (2.1 mmol,

1.35 mL). The soln was cooled to −70 °C and the diethyl methylphosphonate (2 mmol, 304 mg) in THF (8 mL) was added. The resulting mixture was stirred for 15 min. Then α-ketoester **4** (2 mmol) in THF (10 mL) was added at −70 °C. The resulting mixture was stirred for 60 min before it was slowly allowed to warm to −35 °C. The soln was quenched with a saturated HCl ether soln at this temperature. Few minutes later, water (10 mL) was added and then the mixture was allowed to warm to room temperature. The aq layer was extracted with CH_2Cl_2 (3 × 15 mL), the organic layer was dried (Na_2SO_4) and the solvents were evaporated under diminished pressure. The crude product was purified on a silicagel column with 1:1 EtOAc–hexane to give **5**.

3.1.1. 2-*C*-(Diethoxy-phosphorylmethyl)-3-deoxy-4,5:6,7-di-*O*-isopropylidene-D-*gluco*-heptonic acid methyl ester/2-*C*-(diethoxy-phosphorylmethyl)-3-deoxy-4,5:6,7-di-*O*-isopropylidene-D-*manno*-heptonic acid methyl ester 5ac/5′ac. Compound **5ac**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.30–1.41 (m, 18H, Me_2C, CH_3CH$_2$O), 2.07–2.60 (m, 4H, H-3, H-3′, CH_2P), 3.54 (dd, $^3J_{H5-H4} = {}^3J_{H5-H6}$ 7 Hz, 1H, H-5), 3.77 (s, 3H, COOCH_3), 4.10–4.30 (m, 8H, H-4, H-6, H-7, CH$_3$CH_2O); ^{31}P NMR ($CDCl_3$, 101.6 MHz): δ 23.78; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.0 ($^3J_{C-P}$ 16 Hz, *C*H$_3$CH$_2$O), 26.3, 26.5, 26.6, 26.7 (Me_2C), 36.2 (d, $^1J_{C-P}$ 140 Hz, *C*H$_2$P), 44.5 (d, $^3J_{C3-P}$ 16 Hz, C-3), 52.2 (COO*Me*), 61.5 (d, $^2J_{C-P}$ 6 Hz, CH$_3$*C*H$_2$O), 67.1 (C-7), 72.5 (d, $^2J_{C2-P}$ 6 Hz, C-2), 76.3, 76.4 (C-5, C-6), 80.8 (C-4), 108.9, 109.2 (Me$_2$*C*), 174.2 (d, $^3J_{C1-P}$ 5 Hz, C-1).

Compound **5′ac**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.30–1.41 (m, 18H, Me_2C, CH_3CH$_2$O), 2.07–2.60 (m, 4H, H-3, H-3′, CH_2P), 3.54 (dd, $^3J_{H5-H4} = {}^3J_{H5-H6}$ 7 Hz, 1H, H-5), 3.81 (s, 3H, COOCH_3), 4.10–4.30 (m, 8H, H-4, H-6, H-7, CH$_3$CH_2O); ^{31}P NMR ($CDCl_3$, 101.6 MHz): δ 24.45; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.0 ($^3J_{C-P}$ 16 Hz, *C*H$_3$CH$_2$O), 26.3, 26.5, 26.6, 26.7 (Me_2C), 34.9 (d, $^1J_{C-P}$ 140 Hz, *C*H$_2$P), 43.0 (d, $^3J_{C3-P}$ 15 Hz, C-3), 52.3 (COO*Me*), 61.5 (d, $^2J_{C-P}$ 6 Hz, CH$_3$*C*H$_2$O), 67.1 (C-7), 73.9 (d, $^2J_{C2-P}$ 6 Hz, C-2), 74.9, 76.5 (C-5, C-6), 80.8 (C-4), 108.9, 109.2 (Me$_2$*C*), 174.3 (d, $^3J_{C1-P}$ 5 Hz, C-1); FAB + MS: *m*/*z* 455.4 (MH$^+$, 100%); IR, *v* (C=O): 1746 cm^{-1}.

3.1.2. 2-*C*-(Diethoxy-phosphorylmethyl)-3-deoxy-4,5:6,7-di-*O*-isopropylidene-D-*gluco*-heptonic acid isopropyl ester/2-*C*-(diethoxy-phosphorylmethyl)-3-deoxy-4,5:6,7-di-*O*-isopropylidene-D-*manno*-heptonic acid isopropyl ester 5ad/5′ad. Compound **5ad**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.26–1.41 (m, 24H, Me_2C, CH_3CH$_2$O, CH(CH_3)$_2$), 1.90–2.60 (m, 4H, H-3, H-3′, CH_2P), 3.52 (m, 1H, H-5), 4.10–4.30 (m, 8H, H-4, H-6, H-7, CH$_3$CH_2O), 5.09 (COOC*H*); ^{31}P NMR ($CDCl_3$, 101.6 MHz): δ 24.08; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.1 ($^3J_{C-P}$ 16 Hz, *C*H$_3$CH$_2$O), 21.4, 21.5 (CH(*C*H$_3$)$_2$), 26.3, 26.5, 26.6, 26.7 (Me_2C), 36.5 (d, $^1J_{C-P}$ 140 Hz, *C*H$_2$P), 44.1 (d, $^3J_{C3-P}$ 15 Hz, C-3), 61.4 (m, CH$_3$*C*H$_2$O), 67.4 (C-7), 69.8 (COO*C*H), 72.6 (d, $^2J_{C2-P}$ 6 Hz, C-2), 75.2, 76.6 (C-5, C-6), 80.8 (C-4), 109.0, 109.4 (Me$_2$*C*), 173.4 (d, $^3J_{C1-P}$ 5 Hz, C-1).

Compound **5′ad**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.26–1.41 (m, 24H, Me_2C, CH_3CH$_2$O, CH(CH_3)$_2$), 1.90–2.60 (m, 4H, H-3, H-3′, CH_2P), 3.52 (m, 1H, H-5), 4.10–4.30 (m, 8H, H-4, H-6, H-7, CH$_3$CH_2O), 5.09 (COOC*H*); ^{31}P NMR ($CDCl_3$, 101.6 MHz): δ 24.57; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 16.1 (*C*$_3$CH$_2$O, $^3J_{C-P}$ 16 Hz), 21.4, 21.5 (CH(*C*H$_3$)$_2$), 26.3, 26.5, 26.6, 26.7 (Me_2C), 35.1 (d, $^1J_{C-P}$ 140 Hz, *C*H$_2$P), 43.1 (d, $^3J_{C3-P}$ 15 Hz, C-3), 61.4 (m, CH$_3$*C*H$_2$O), 67.5 (C-7), 69.3 (COO*C*H), 74.1 (d, $^2J_{C2-P}$ 6 Hz, C-2), 75.2, 76.6 (C-5, C-6), 81.1 (C-4), 109.4, 109.6 (Me$_2$*C*), 173.5 (d, $^3J_{C1-P}$ 5 Hz, C-1). FAB + MS: *m*/*z* 483.5 (MH$^+$, 100%); IR, *v* (C=O): 1726 cm^{-1}.

3.1.3. 2-*C*-(Diethoxy-phosphorylmethyl)-3-deoxy-4,5:7,8-di-*O*-isopropylidene-6-dimethyl-*tert*-butylsilyl-D-*glycero*-D-*gulo*-octonic acid methyl ester/2-*C*-(diethoxy-phosphorylmethyl)-3-deoxy-4,5:7,8-di-*O*-isopropylidene-6-dimethyl-*tert*-butylsilyl-D-*glycero*-D-*ido*-octonic acid methyl ester 5bc/5′bc. Compound **5bc**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.10 (s, 3H, SiMe_2), 0.12 (s, 3H, SiMe_2), 0.89 (s, 9H, Si-*t*-*Bu*), 1.20–1.50 (m, 18, Me_2C, CH_3CH$_2$O), 1.90–2.6 (m, 4H, H-3, H-3′, CH_2P), 3.77 (s, 3H, CH_3OOC), 3.60–4.20 (m, 10H, H-4, H-5, H-6, H-7, H-8, CH$_3$CH_2O); ^{31}P NMR ($CDCl_3$, 101.6 MHz): δ 24.48; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ −4.9, −4.7 (SiMe_2), 15.7 (*C*H$_3$CH$_2$O), 17.6 (Si–*t*-C(*Me*)$_3$), 25.4 (Si–*t*-*C*(Me)$_3$), 24.5, 25.8, 26.3, 26.5 (Me_2C), 36.0 (d, $^1J_{C-P}$ 140 Hz, *C*H$_2$P), 44.3 (d,$^3J_{C3-P}$ 16 Hz, C-3), 51.9 (COO*Me*), 60.7 (d, $^2J_{C-P}$ 6 Hz, CH$_3$*C*H$_2$O), 65.4 (C-8), 71.5, 72.8 (C-6, C-7), 72.4 (d, $^2J_{C2-P}$ 5 Hz, C-2), 75.8 (C-5), 82.3 (C-4), 108.0, 108.3 (Me$_2$*C*), 174.0 (d, $^3J_{C1-P}$ 9 Hz, C-1).

Compound **5′bc**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.10 (s, 3H, SiMe_2), 0.12 (s, 3H, SiMe_2), 0.91 (s, 9H, Si-*t*-*Bu*), 1.20–1.50 (m, 18H, Me_2C, CH_3CH$_2$O), 1.90–2.35, 2.4–2.6 (m, 4H, H-3, H-3′, CH_2P), 3.80 (s, 3H, CH_3OOC), 3.60–4.20 (m, 10H, H-4, H-5, H-6, H-7, H-8, CH$_3$CH_2O); ^{31}P NMR ($CDCl_3$, 101.6 MHz): δ 23, 79; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ −4.9, −4.7 (SiMe_2), 15.7 (*C*H$_3$CH$_2$O), 17.6 (Si-*t*-C(*Me*)$_3$), 25.4 (Si-*t*-*C*(Me)$_3$), 24.5, 25.8, 26.3, 26.5 (Me_2C), 34.8 (d, $^1J_{C-P}$ 140 Hz,*C*H$_2$P), 42.8 (d, $^3J_{C3-P}$ 15 Hz, C-3), 51.9 (COO*Me*), 61.4 (d, $^2J_{C-P}$ 6 Hz, CH$_3$*C*H$_2$O), 65.7 (C-8), 71.8, 72.0 (C-6, C-7), 73.8 (d, $^2J_{C2-P}$ 5 Hz, C-2), 75.7 (C-5), 82.6 (C-4), 107.8, 108.0 (Me$_2$*C*), 174.0 (d, $^3J_{C1-P}$ 9 Hz, C-1); FAB + MS: *m*/*z* 599.7 (MH$^+$, 50%); IR, *v* (C=O): 1741 cm^{-1}.

3.1.4. 2-*C*-(Diethoxy-phosphorylmethyl)-3-deoxy-4,5:7,8-di-*O*-isopropylidene-6-dimethyl-*tert*-butylsilyl-D-*glycero*-D-*gulo*-octonic acid isopropyl ester/2-*C*-(diethoxy-phosphorylmethyl)-3-deoxy-4,5:7,8-di-*O*-isopropylidene-6-dimethyl-*tert*-butylsilyl-D-*glycero*-D-*ido*-octonic acid isopropyl ester 5bd/5′bd. Compound **5bd**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.08 (s, 3H, SiMe_2), 0.12 (s, 3H, SiMe_2), 0.89 (s, 9H, Si*t*-*Bu*), 1.25–1.50 (m, 24H, Me_2C, CH_3CH$_2$O, (CH_3)$_2$CH), 1.90–2.70 (m, 4H, H-3, H-3′, CH_2P), 3.60–4.20 (m, 10H, H-4, H-5, H-6, H-7, H-8, CH$_3$CH_2O), 5.09 (COOC*H*); ^{31}P NMR ($CDCl_3$, 101.6 MHz): δ 23.89; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ −4.0, −3.9 (SiMe_2), 16.1 ($^3J_{C-P}$ 16 Hz, *C*H$_3$CH$_2$O), 18.1 (Si-*t*-C(*Me*)$_3$), 21.4, 21.5 (CH(*C*H$_3$)$_2$), 25.8 (Si-*t*-*C*(Me)$_3$), 24.9, 26.2, 26.6, 27.2 (*Me*$_2$C), 34.8 (d, $^1J_{C-P}$ 140 Hz, *C*H$_2$P), 43.2 (d, $^3J_{C3-P}$ 15 Hz, C-3), 61.4 (d, $^2J_{C-P}$ 6 Hz, CH$_3$*C*H$_2$O), 66.1 (C-8), 69.5 (COO*C*H), 71.9, 72.3 (C-6, C-7), 73.4 (d, $^2J_{C2-P}$ 6 Hz, C-2), 76.0 (C-5), 82.9 (C-4), 108.3, 108.7 (Me$_2$*C*), 173.7 (d, $^3J_{C1-P}$ 5 Hz, C-1).

Compound **5′bd**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.08 (s, 3H, SiMe_2), 0.12 (s, 3H, SiMe_2), 0.89 (Si-*t*-*Bu*, s, 9H), 1.25–1.50 (m, 24H, Me_2C, CH_3CH$_2$O, (CH_3)$_2$CH), 1.90–2.70 (m, 4H, H-3, H-3′, CH_2P), 3.60–4.20 (m, 10H, H-4, H-5, H-6, H-7, H-8, CH$_3$CH_2O), 5.09 (COOC*H*); ^{31}P NMR ($CDCl_3$, 101.6 MHz): δ 24.87; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ −4.0, −3.9 (SiMe_2), 16.1 (*C*H$_3$CH$_2$O, $^3J_{C-P}$ 16 Hz), 18.1 (Si-*t*-C(*Me*)$_3$), 21.4, 21.5 (CH(*C*H$_3$)$_2$), 25.8 (Si-*t*-*C*(Me)$_3$), 24.9, 26.2, 26.6, 27.2 (*Me*$_2$C), 36.7 (d, $^1J_{C-P}$ 140 Hz, *C*H$_2$P), 44.3 (d, $^3J_{C3-P}$ 15 Hz, C-3), 61.4 (d, $^2J_{C-P}$ 6 Hz, CH$_3$*C*H$_2$O), 65.8 (C-8), 69.5 (COO*C*H), 71.8, 73.1 (C-6, C-7), 72.6 (d, $^2J_{C2-P}$ 6 Hz, C-2), 76.2 (C-5), 82.3 (C-4), 108.9, 108.9 (Me$_2$*C*), 173.4 (d, $^3J_{C1-P}$ 5 Hz, C-1); FAB + MS: *m*/*z* 627.8 (MH$^+$, 100%); IR, *v* (C=O): 1741 cm^{-1}.

3.1.5. Complete deprotection of hydroxyphosphonates 5/5′ into 6/6′. One step procedure: Me_3SiBr (2.30 mmol, 352 mg) was added to a soln of **5** (0.60 mmol) in 1,2-dichloroethane (3.0 mL). After stirring for 6 h at room temperature the reaction mixture was concentrated under diminished pressure. Then MeOH (3.0 mL) was added to the crude residue and stirring was pursued for 15 h at room temperature. After evaporation, the crude residue was washed with CH_2Cl_2 (×2) and diethylether (×1) before it was lyophilized to yield the hygroscopic solid **6**.

Two steps procedure: Me_3SiBr (1.90 mmol, 291 mg) was added at 5 °C to a mixture of **5** (0.36 mmol) and Et_3N (4.80 mmol, 486 mg) in CH_2Cl_2 (2.0 mL). After stirring for 18 h at room temperature, the reaction mixture was concentrated under diminished pressure. The crude residue was dissolved in EtOAc (20 mL) and water (20 mL) was added. After stirring for 6 h the organic layer was separated, then dried over sodium sulfate. After filtration, the solvent was removed under diminished pressure to yield the crude colourless oil **7**.

In a second step, the partially protected phosphonic acid **7** (0.41 mmol) was dissolved in MeCN (12 mL). Molecular sieves (0.5 g, 4 Å) and dry Amberlyst 15 (0.5 g) were added. After stirring for 18 h the mixture was filtered and the organic layer was evaporated under diminished pressure to afford the crude **6**.

3.1.6. 2-*C*-Phosphonomethyl-3-deoxy-D-*gluco*-heptonic acid/2-*C*-phosphonomethyl-3-deoxy-D-*manno*-heptonic acid 6e/6′e. Compound **6e**: ^{1}H NMR (D_2O, 250 MHz): δ 2.20–2.80 (m, 4H, H-3, H-3′, CH_2P), 3.60–4.00 (m, 5H, H-4, H-5, H-6, H-7); ^{31}P NMR (D_2O, 101.6 MHz): δ 22.98; ^{13}C NMR (D_2O, 62.9 MHz): δ 34.1 (d, $^1J_{C-P}$ 135.5 Hz, *C*H$_2$P), 36.8 (C-3), 63.3 (C-7), 70.9, 71.7 (C-5, C-6), 74.2 (d, $^2J_{C2-P}$ 3.7 Hz, C-2), 78.8 (C-4) 178.6 (d, $^3J_{C1-P}$ 15.9 Hz, C-1).

Compound **6′e**: ^{1}H NMR (D_2O, 250 MHz): δ 2.20–2.80 (m, 4H, H-3, H-3′, CH_2P), 3.60–4.00 (m, 5H, H-4, H-5, H-6, H-7); ^{31}P NMR (D_2O, 101.6 MHz): δ 21.34; ^{13}C NMR (D_2O, 62.9 MHz): δ 34.6 (d, $^1J_{C-P}$ 136.7 Hz, *C*H$_2$P), 36.6 (C-3), 63.3 (C-7), 71.1, 71.4 (C-5, C-6), 74.1 (d, $^2J_{C2-P}$ 3.7 Hz, C-2), 77.4 (C-4), 180.1 (d, $^3J_{C1-P}$ 12.2 Hz, C-1).

3.1.7. 2-*C*-Phosphonomethyl-3-deoxy-D-*glycero*-D-*gulo*-octonic acid/2-*C*-phosphonomethyl-3-deoxy-D-*glycero*-D-*ido*-octonic acid 6f/6′f. Compound **6f**: ^{1}H NMR (CD_3OD, 250 MHz): δ 2.10–2.60 (m, 4H, CH_2-3, CH_2P), 3.50–4.00 (m, 5H, H-5, H-6, H-7, CH_2-8), 4.60–4.90 (m, 1H, H-4); ^{31}P NMR (CD_3OD, 101.6 MHz): δ 21.83; ^{13}C NMR (CD_3OD, 62.9 MHz): δ 35.3 (d, $^1J_{C-P}$ 137.9 Hz *C*H$_2$P), 38.3, (C-3), 64.6 (C-8), 71.4, 72.4 (C-6, C-7), 73.6 (d, $^2J_{C2-P}$ 7.3 Hz, C-2), 80.3 (C-5), 82.0 (C-4), 178.3 (d, $^3J_{C1-P}$ 13.4 Hz, C-1).

Compound **6′f**: ^{1}H NMR (CD_3OD, 250 MHz): δ 2.10–2.60 (m, 4H, CH_2-3, *C*H$_2$P), 3.50–4.00 (m, 5H, H-5, H-6, H-7, CH_2-8), 4.60–4.90 (m, 1H, H-4); ^{31}P NMR (CD_3OD, 101.6 MHz): δ 23.30; ^{13}C NMR (CD_3OD, 62.9 MHz): δ 35.3 (d, $^1J_{C-P}$ 137.9 Hz *C*H$_2$P), 38.9 (C-3), 64.6 (C-8), 71.4, 72.4 (C-6, C-7), 73.6 (d, $^2J_{C2-P}$ 7.3 Hz, C-2), 80.3 (C-5), 82.0 (C-4), 179.8 (d, $^3J_{C1-P}$ 12.2 Hz, C-1).

3.1.8. 2-*C*-Phosphonomethyl-3-deoxy-4,5:7,8-di-*O*-isopropylidene-6-dimethyl-*tert*-butylsilyl-D-*glycero*-D-*gulo*-octonic acid methyl ester/2-*C*-phosphonomethyl-3-deoxy-4,5:7,8-di-*O*-isopropylidene-6-dimethyl-*tert*-butylsilyl-D-*glycero*-D-*ido*-octonic acid methyl ester 7bc/7′bc. Compound **7bc**: ^{1}H NMR (CD_3COCD_3, 250 MHz): δ 0.18 (s, 6H, SiMe_2); 0.96 (s, 9H, Si-*t*-*Bu*), 1.33 (s, 3H, Me_2C), 1.41 (s, 3H, Me_2C), 1.90–2.80 (m, 4H, CH_2-3, CH_2P), 3.77 (s, 3H, *Me*O), 3.60–4.40 (m, 6H, H-4, H-5, H-6, H-7, CH_2-8). ^{31}P NMR (CD_3COCD_3, 101.6 MHz): δ 28.75. ^{13}C NMR (CD_3COCD_3, 62.9 MHz): δ −4.3, −4.4 (SiMe_2), 18.4 (Si-*t*-C(*Me*)$_3$), 24.8, 26.0, 26.2, 26.8, 27.0 (Me_2C, Si-*t*-*C*(Me)$_3$),

33.0–37.0 (CH_2P), 43.8 (C-3), 52.5 (COO*Me*), 65.5 (CH_2O), 65.4 (C-8), 72.3 (C-6), 73.3 (C-2), 73.8 (C-7), 76.7 (C-5), 83.1 (C-4), 108.2, 108.6 (Me_2C), 174.9 (C-1); FAB + MS: *m/z* 543 (MH^+, 100%).

Compound **7′bc**: ^{1}H NMR (CD_3COCD_3, 250 MHz): δ 3.79 (s, 3H, *Me*O); ^{31}P NMR (CD_3COCD_3, 101.6 MHz): δ 21.83; ^{13}C NMR (CD_3COCD_3, 62.9 MHz): δ 45.7 (C-3), 65.8 (CH_2O), 74.6. (C-2), 108.4, 109.0 (Me_2C). FAB + MS: *m/z* 543 (MH^+, 100%).

3.1.9. 2-*C*-Phosphonomethyl-3-deoxy-4,5:7,8-di-*O*-isopropylidene-6-dimethyl-*tert*-butylsilyl-D-*glycero*-D-*gulo*-octonic acid isopropyl ester/2-*C*-phosphonomethyl-3-deoxy-4,5:7,8-di-*O*-isopropylidene-6-dimethyl-*tert*-butylsilyl-D-*glycero*-D-*ido*-octonic acid isopropyl ester 7bd/7′bd. ^{1}H NMR (CD_3COCD_3, 250 MHz): δ 0.19 (s, 3H, Si*Me*$_2$), 0.22 (s, 3H, Si*Me*$_2$), 0.96 (s, 9H, Si-*t*-*Bu*), 1.30–1.42 (m, 18H, *Me*$_2$C, *Me*$_2$CH), 2.00–2.40 (m, 4H, CH_2-3, CH_2P), 3.60–4.40 (m, 6H, H-4, H-5, H-6, H-7, CH_2-8), 5.00–5.20 (H, 1H, Me$_2$C*H*); FAB + MS: *m/z* 571 (MH^+, 100%).

Compound **7bd**: ^{31}P NMR (CD_3COCD_3, 101.6 MHz): δ 28.67; ^{13}C NMR (CD_3COCD_3, 62.9 MHz): δ −4.3, −4.4 (Si*Me*$_2$), 18.4 (Si-*t*-*C*(Me)$_3$), 21.5 (CH*Me*$_2$), 26.3 (Si-*t*-C(*Me*)$_3$), 24.8, 26.0, 27.0, 27.1 (*Me*$_2$C), 33.0–37.0 (CH_2P), 45.2 (d, $^3J_{C-P}$ 15.0 Hz, C-3), 65.7 (CH_2O), 69.7 (*C*HMe$_2$), 72.4 (C-6), 73.8 (C-7), 76.6 (C-5), 74.3 (CH_2P), 83.1 (C-4), 108.4, 109.1 (Me_2C), 174.1 (C-1).

Compound **7′bd**: ^{31}P NMR (CD_3COCD_3, 101.6 MHz): δ 21.73; ^{13}C NMR (CD_3COCD_3, 62.9 MHz): δ −4.3, −4.4 (Si*Me*$_2$), 18.4 (Si-*t*-*C*(Me)$_3$), 21.5 (CH*Me*$_2$), 26.3 (Si-*t*-C(*Me*)$_3$), 24.8, 26.0, 27.0, 27.1 (*Me*$_2$C), 33.0–37.0 (CH_2P), 43.9 (d, $^3J_{C-P}$ 14.0 Hz, C-3), 65.4 (CH_2O), 69.8 (*C*HMe$_2$), 72.2 (C-6), 73.2 (CH_2P), 73.8. (*C-7*), 76.8 (C-5), 83.0 (C-4), 108.3, 108.6 (Me_2C), 173.9 (C-1).

3.1.10. Partial deprotection of hydroxyphosphonates 5 into 8/8′. Me_3SiBr (0.28 mmol, 43 mg) was added to MeOH (11 mL). After stirring 1 h at room temperature, the hydroxyphosphonate **5** (0.6 mmol) was added. After stirring for 15 h, the mixture was concentrated under diminished pressure. The obtained residue was successively co-evaporated with CH_2Cl_2 (10 mL), acetone (10 mL) and diethylether (10 mL) to afford the hygroscopic solid **8**.

3.1.11. 2-*C*-Diethoxyphosphorylmethyl-3-deoxy-D-*gluco*-heptonic acid/2-*C*-diethoxyphosphorylmethyl-3-deoxy-D-*manno*-heptonic acid 8e/8′e. Compound **8e**: ^{1}H NMR (CD_3COCD_3, 250 MHz): δ 1.20–1.40 (m, 6H, CH_3CH$_2$O), 2.30–3.00 (m, 4H, H-3, H-3′, CH_2P), 3.90–4.20 (m, 8H, H-5, H-6, H-7, CH$_3$CH_2O), 4.80–4.90 (m, 1H, H-4); ^{31}P NMR (CD_3COCD_3, 101.6 MHz): δ 28.61; ^{13}C NMR (CD_3COCD_3, 62.9 MHz): δ 34.1 (d, $^1J_{C-P}$ 135.5 Hz,*C*H$_2$P), 36.8 (C-3), 63.3 (C-7), 70.9, 71.7 (C-5, C-6), 74.2 (d, $^2J_{C2-P}$ 3.7 Hz, C-2), 78.8 (C-4), 178.6 (d, $^3J_{C1-P}$ 15.9 Hz, C-1).

Compound **8′e**: ^{1}H NMR (CD_3COCD_3, 250 MHz): δ 2.20–2.80 (m, 4H, H-3, H-3′, CH_2P), 3.60–4.00 (m, 5H, H-4, H-5, H-6, H-7); ^{31}P NMR (CD_3COCD_3, 101.6 MHz): δ 29.63; ^{13}C NMR (CD_3COCD_3, 62.9 MHz): δ 34.6 (d, $^1J_{C-P}$ 136.7 Hz, *C*H$_2$P), 36.6 (C-3), 63.3 (C-7), 71.1, 71.4 (C-5, C-6), 74.1 (d, $^2J_{C2-P}$ 3.7 Hz, C-2), 77.4 (C-4), 180.1 (d, $^3J_{C1-P}$ 12.2 Hz, C-1).

3.1.12. 2-*C*-Diethoxyphosphorylmethyl-3-deoxy-D-*glycero*-D-*gulo*-octonic acid/2-*C*-diethoxyphosphorylmethyl-3-deoxy-D-*glycero*-D-*ido*-octonic acid 8f/8′f. Compound **8f**: ^{1}H NMR (CD_3COCD_3, 250 MHz): δ 1.20–1.40 (m, 6H, CH_3CH$_2$O), 2.30–3.10 (m, H-3, H-3′, CH_2P), 3.90–4.20 (m, 9H, H-5, H-6, H-7, H-8, CH$_3$CH_2O), 4.70–4.80 (m, 1H, H-4); ^{31}P NMR (D_2O, 101.6 MHz): δ 28.29; ^{13}C NMR (CD_3COCD_3, 62.9 MHz): δ 34.1 (d, $^1J_{C-P}$ 140.4 Hz, *C*H$_2$P), 39.0 (C-3), 62.4 (d, $^2J_{C-P}$ 4.9 Hz, CH$_3$CH_2O), 68.1 (C-8), 72.9 (C-2), 74.9 (C-2), 75.6, 77.8, 77.9 (C-6, C-7, C-8), 81.4 (C-4), 176.2 (C-1).

Compound **8′f**: ^{1}H NMR (CD_3COCD_3, 250 MHz): δ 1.20–1.40 (m, 6H, CH_3CH$_2$O), 2.30–3.10 (m, 4H, H-3, H-3′, CH_2P), 3.90–4.20 (m, 9H, H-5, H-6, H-7, H-8, CH$_3$CH_2O), 4.70–4.80 (m, 1H, H-4); ^{31}P NMR (D_2O, 101.6 MHz): δ 29.52; ^{13}C NMR (CD_3COCD_3, 62.9 MHz): δ 33.2 (d, $^1J_{C-P}$ 140.4 Hz, *C*H$_2$P) 38.2 (C-3) 62.9 (d, $^2J_{C-P}$ 4.9 Hz, CH$_3$CH_2O), 68.1 (C-8), 73.6 (C-2), 75.6, 77.8, 77.9 (C-6, C-7, C-8), 81.8 (C-4), 177.2 (C-1).

4. Biological studies

The bacterial strains tested were *E. coli* (CIP 7624), *Y. enterocolitica* (CIP 15728), *P. aeruginosa* (CIP 76110), *S. aureus* (ATCC 6538) and *B. subtilis* (ATCC 9524).

Antibacterial tests were performed by the disk diffusion method according to Jorgensen et al.[11] Petri dishes of Mueller–Hinton agar (Difco) were inoculated by spreading the bacterial inoculum (10^7 CFU/mL in physiological water) over the entire surface of the agar. Sterile 10 mm diameter disks were impregnated with 75 μg derivatives and placed onto the agar surface. The dishes were incubated at 37 °C for 24 h. The diameters of the zone inhibition were measured and compared with control. Results are the mean of three experiments for each derivative and bacterial strain.

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