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# Synthesis of α-Aryl-Substituted and Conformationally Restricted Fosmidomycin Analogues as Promising Antimalarials

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Fosmidomycin represents a new antimalarial drug that acts by inhibition of 1-deoxy-D-xylulose 5-phosphate reductoisomerase, an essential enzyme of the mevalonate-independent pathway of isoprenoid biosynthesis. This work describes the synthesis of a series of α-aryl-substituted fosmidomycin analogues that exhibit improved antimalarial activity. A linear synthetic route involving a 3-aryl-3-phosphorylpropanal intermediate proved practical to prepare these derivatives. A phospha-Michael addition to cyclopent-2-enone gave access to conformationally restricted analogues.


## Introduction

In the 1970s, Okuhura and colleagues reported the first isolation of fosmidomycin as a structurally simple antibiotic from *Streptomyces lavendulae*. In recent years, fosmidomycin received considerable attention due to its promising antimalarial activity, and recent clinical trials conducted in Gabon and Thailand confirmed the potential of fosmidomycin as an antimalarial drug.[1,2] In 1998, the molecular target of fosmidomycin was discovered to be 1-deoxy-D-xylulose 5-phosphate (DOXP) reductoisomerase.[3,4] This enzyme plays an essential role in the mevalonate-independent pathway for the synthesis of isoprenoids, and is absent in humans.[5] Fosmidomycin was found to be a potent inhibitor for the DOXP reductoisomerase (DXR) of *P. falciparum*.[6] After this important discovery, much attention has been focused on the chemical synthesis of fosmidomycin analogues. FR900098, the acetyl analogue of fosmidomycin, was shown to be approximately twice as active against *P. falciparum* in vitro, as well as in a *P. vinckei* mouse model.[6]

Chemical variations of fosmidomycin were mainly directed to increase the inhibitory activity against DXR or to achieve inhibitors with improved physicochemical properties. To study the structure-activity relationships, hydroxamic moiety modifications, including benzoxazolone and oxazolopyridinone functionalities, have been reported.[7] Also, the phosphonate moiety has been altered to produce prodrugs with improved oral bioavailability.[8–10]

Surprisingly, modifications addressing the three-carbon spacer are scarce. Recently, we reported the discovery of a series of α-aryl-substituted fosmidomycin or FR900098 derivatives, **1** and **2** (Figure 1), which generally proved superior to fosmidomycin in inhibiting *P. falciparum* growth.[11] To sort out the influence of the lipophilicity and electronic properties of this phenyl moiety, substituents were introduced according to Topliss' methodology.[12] Briefly, in this methodology an operational scheme is used to quickly identify the optimum substitution on a benzene ring for maximizing drug potency by virtue of resulting changes in hydrophobic, electronic and steric effects.

Here, we describe the detailed procedure used to synthesize these α-substituted analogues. Although strategies to synthesise products with a C–P bond are well documented,[13] introducing aryl substituents in the α-position of a phosphonate [resulting in a P–CH(Ar)–C motif] is quite challenging. Fosmidomycin was first synthesised in the early 1980s by Hemmi et al. using a Michaelis–Becker reaction.[14] This approach cannot be easily adapted to allow the synthesis of α-substituted derivatives.

In this study, 3-aryl-substituted 3-phosphorylpropanals were anticipated to be appropriate intermediates for the synthesis of a small series of α-aryl-substituted fosmidomycin analogues. Depending on the availability of the starting material, a lithiation/allylation/alkene oxidation sequence or a Michael addition will be considered for the synthesis of these intermediates (Scheme 1). A drawback of this strat-

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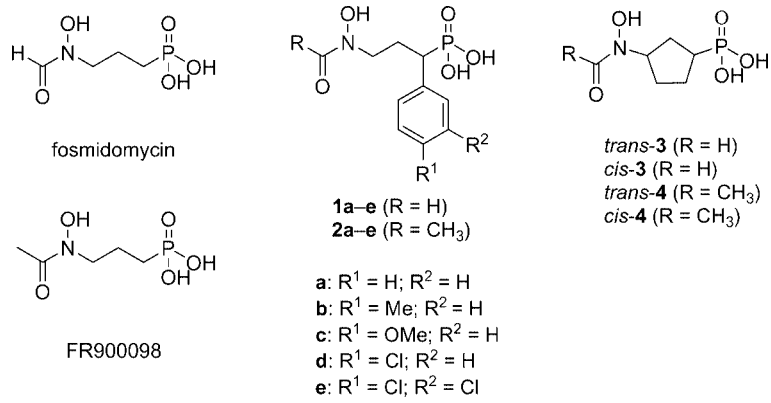
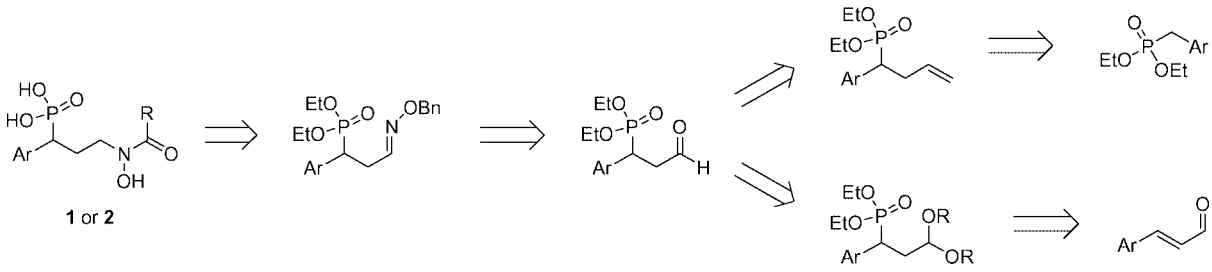



Figure 1. Structures of fosmidomycin, FR900098 and analogues under study.




Scheme 1. Retrosynthetic route toward analogues **1** and **2**.

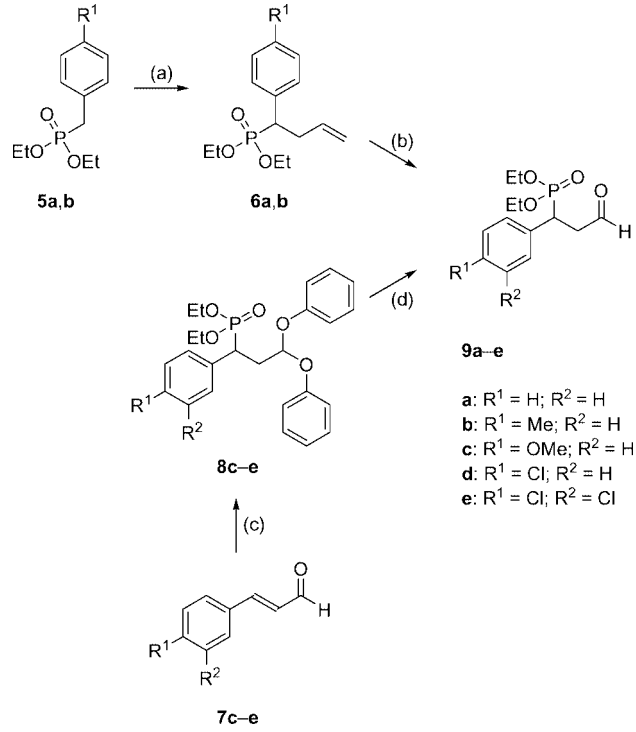
egy is that every derivative has to be synthesized de novo, which does not permit preparation of an extended series of the envisaged analogues. However, when the proposed routes give the desired analogues in good overall yields, they might be valuable for scale-up purposes, e.g., to prepare a selected inhibitor for in vivo studies. Interestingly, when applied to cyclopent-2-enone, the Michael addition should be a useful approach in designing unprecedented fosmidomycin analogues **3** and **4**, in which the three-carbon spacer is part of a cyclopentane ring. Indeed, by incorporating the α- and β-carbon atoms into a cyclopropane ring, we recently demonstrated that rigidification of fosmidomycin might result in potent DXR inhibitors.[15]

## Results and Discussion

### Synthesis of α-Aryl-Substituted Fosmidomycin and FR900098 Analogues

Retrosynthetic analysis toward the synthesis of the desired α-substituted fosmidomycin analogues is depicted in Scheme 1.

Two synthetic pathways toward the aldehyde synthons were followed (Scheme 2). The first one started from the appropriate diethyl benzylphosphonate, which upon treatment with *n*BuLi in the presence of allyl bromide, afforded **6a**,**b** in 97 and 33% yields, respectively.[16] Oxidation of **6a**,**b** to the vicinal *cis*-diol with osmium tetraoxide in the pres-




Scheme 2. Reagents and conditions: (a) (i) *n*BuLi, THF, –50 to –70 °C, (ii) allyl bromide, –70 °C; (b) (i) $OsO_4$, 4-methylmorpholine *N*-oxide, dioxane (ii) $NaIO_4$; (c) triethyl phosphite, phenol, 100 °C; (d) 2 N HCl, room temperature.

ence of 4-methylmorpholine *N*-oxide, followed by sodium periodate cleavage gave aldehydes **9a**,**b**, which could be used in the next step without further purification.

When the desired benzylphosphonate was not commercially available, an alternative strategy to prepare the desired aldehydes was followed. A 1,4-addition of triethyl phosphite to the appropriately substituted cinnamaldehyde in the presence of phenol gave the acetals **8c**–**e** in 70–85% yield.[17] Subsequent deprotection of the diphenyl acetal afforded in 76–83% yield the corresponding aldehydes, which appeared stable enough to be purified by flash chromatography. If necessary, substituted cinnamaldehydes were synthesized. In our hands a palladium-catalyzed synthesis from acrolein diethyl acetal and the corresponding aryl iodide was very efficient.[18] Only the (*E*) isomer was obtained, as deduced from the large coupling (16 Hz) between the vinylic hydrogen atoms.

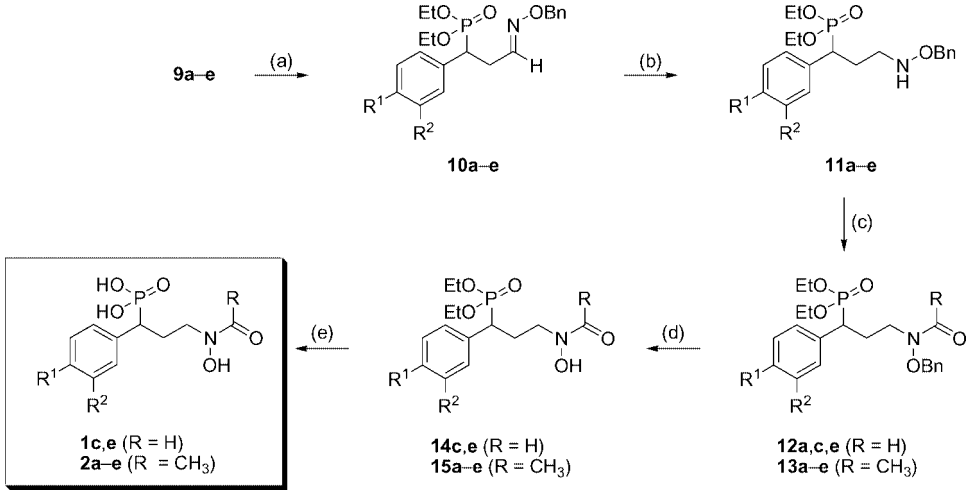
Conversion of the appropriate aldehydes to the desired analogues **1** and **2** is depicted in Scheme 3. Treatment of **9a**–**e** with *O*-benzylhydroxylamine yielded (67–92%) oximes **10a**–**e**. $^{13}C$ NMR spectroscopy revealed the presence of two geometric isomers, which were reduced with sodium cyanoborohydride to produce the benzyloxyamines **11a**–**e** in 91–96% yield. Subsequent acetylation of **11a**–**e** with acetyl chloride afforded **13a**–**e** in good yield. Different methods were investigated for the formylation of **11**. Since the mixed anhydride method was unsuccessful, compound **11a** was formylated with 2-thioxothiazolidine-3-carbaldehyde, prepared by reaction between 2-mercaptothiazoline and formic acid using DCC as coupling agent. A drawback of this approach was the long reaction time (more than 3 d at room temperature). Consequently, **11c**,**d**,**e** were formylated using formic acid and 1,1′-carbonyldiimidazole in dichloromethane. This method reduced the reaction time considerably.

Benzyl deprotection by catalytic hydrogenation proved tricky, especially in the formyl series, where this reaction generally led to the formation of two reaction products. After their separation, mass spectrometry was useful in assigning these compounds as the desired product and the corresponding deoxygenated derivative, i.e. the amide. Further structural evidence for this deoxygenation was furnished by a $^1H$ COSY NMR spectrum of the side product, which shows a strong coupling between the $NCH_2$ protons and a heteroatom-bound proton at $\delta$ = 7.04 ppm. This coupling is normally absent in the desired products, as may be expected for such long-range $^4J(CH_2NOH)$ coupling. Also, the characteristic $^{13}C$ NMR upfield shifts of the N–$CH_2$ carbon signal are in agreement with the absence of the OH group on the nitrogen atom (β-substituent effect). Indeed, for the deoxygenated product the N–$CH_2$ signal appeared at $\delta$ = 35.8 ppm, while for product **14c** two signals at $\delta$ = 47 and 44 ppm were found. This indicates that **14c** (and also **14e**) exists as a mixture of *syn*- and *anti*-NOH rotamers in a 2:1 ratio.

Compounds **14c**,**e** and **15a**–**e** were finally deprotected with 4 equiv. of TMSBr in $CH_2Cl_2$ at ambient temperature to afford pure **1c**,**e** and **2a**–**e** after purification by reversed-phase HPLC. Although this reaction was almost quantitative, minor amounts of deacylated products were detected, probably due to small amounts of HBr in the TMSBr reagent.

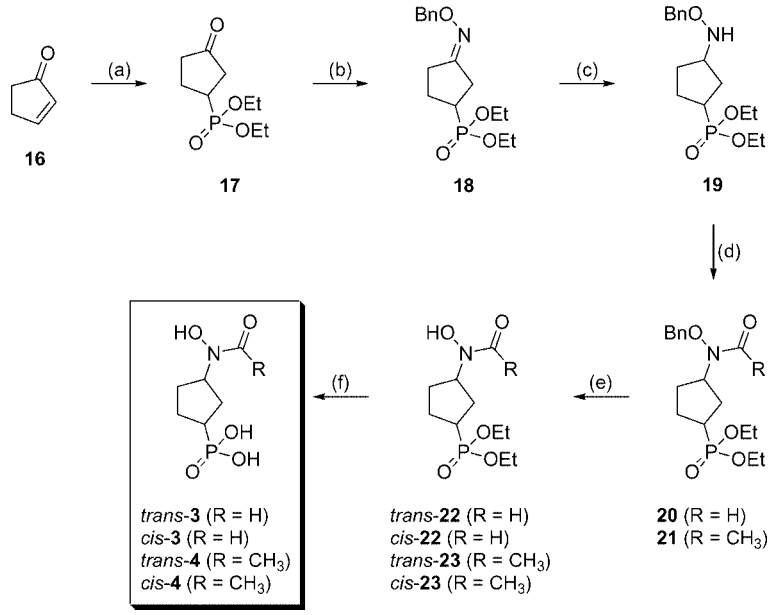
## Synthesis of Conformationally Restricted Fosmidomycin and FR900098 Analogues

The approach used to convert the cinnamaldehydes **7c**–**e** to the corresponding α-substituted fosmidomycin derivatives was also successfully applied to the preparation of four five-membered cyclic fosmidomycin analogues from cyclopent-2-enone (Scheme 4). Michael addition of triethyl phosphite to this cyclic α,β-unsaturated ketone gave direct access to the diethyl 3-oxocyclopentylphosphonate.[17] The remaining part of the synthesis involved the same transformations as used for the α-aryl phosphonates. Separation of the diastereomeric pairs was realized after the hydro-




Scheme 3. Reagents and conditions: (a) *O*-benzylhydroxylamine, pyridine, EtOH, room temperature; (b) $NaCNBH_3$, MeOH, HCl, room temperature; (c) acetyl chloride, $CH_2Cl_2$, $Et_3N$, 0 °C or carbonyldiimidazole, HCOOH, $CH_2Cl_2$, room temperature (or 2-thioxothiazolidine-3-carbaldehyde for **12a**); (d) $H_2$, Pd/C, MeOH, room temperature; (e) TMSBr, $CH_2Cl_2$, room temperature.




Scheme 4. Reagents and conditions: (a) triethyl phosphite, phenol, 100 °C; (b) *O*-benzylhydroxylamine, pyridine, EtOH, room temperature; (c) $NaCNBH_3$, MeOH, HCl, room temperature; (d) acetyl chloride, $CH_2Cl_2$, $Et_3N$, 0 °C or carbonyldiimidazole, HCOOH, $CH_2Cl_2$, room temperature; (e) $H_2$, Pd/C, MeOH, room temperature; (f) TMSBr, $CH_2Cl_2$, room temperature.

genolysis. The *cis* and *trans* isomers were assigned by $^1H$ NOEDIF NMR experiments: an interaction between the NOH group and the methyl groups of the phosphonate ester was observed for *cis*-**22** and *cis*-**23**, as opposed to the *trans* isomer, where such a contact was missing. The $^{13}C$ NMR spectra of compounds **22** further point to the presence of a major and a minor form, probably as a result of restricted rotation in the hydroxamic group, with preferential formation of the *syn* isomer due to a likely hydrogen bond between the NOH group and the carbonyl group.

By using the described procedures, we have synthesized eleven analogues, allowing us to perform initial SAR studies for the α-aryl series.[11] Although these studies revealed that the α-aryl analogues were generally weaker *E. coli* DXR inhibitors than fosmidomycin, these analogues unambiguously surpassed the activity of fosmidomycin in inhibiting *P. falciparum* growth. Remarkably, the formyl analogues **1c** and **1e** consistently outperformed the acetyl derivatives **2c** and **2e**, both in the enzyme and the parasite growth inhibition assays. Compound **1e** emerged as the most promising analogue with an $IC_{50}$ value of 0.036 μM.

Amongst the fosmidomycin analogues in which the C–C–C spacer is part of a cyclopentane ring, the *trans* analogues proved notably more active than the *cis* isomers (Table 1). This is in agreement with recent results obtained with cyclopropane fosmidomycin analogues, where a *trans* orientation of the phosphonate group and the hydroxyamide moiety also yielded the most potent inhibitor.[15] Remarkably, in the cyclopentane series, the inhibitory activity of the formyl analogues surpassed that of the acetyl derivatives, while the opposite trend was observed in the cyclopropane series.

Table 1. Inhibitory activity on *E. coli* DXR enzyme.

| Compound | $IC_{50}$ [μM] |
|---|---|
| Fosmidomycin | 0.029 |
| FR900098 | 0.035 |
| *trans*-**3** | 0.20 |
| *cis*-**3** | 2.3 |
| *trans*-**4** | 2.3 |
| *cis*-**4** | 12 |

## Conclusion

In conclusion, a synthetic procedure for the preparation of α-aryl-substituted fosmidomycin analogues was developed starting from a ring substituted benzylphosphonate. Alternatively, these analogues were also accessible by a Michael addition of triethyl phosphite to an appropriate cinnamaldehyde. The latter method was also successfully used to prepare a series of cyclopentyl analogues of fosmidomycin.

## Experimental Section

**General:** IUPAC names were generated with Chemdraw Ultra 8.0 (Chemoffice 2004, Cambridge Soft, Cambridge, USA). Most reactions were carried out under $N_2$. Precoated Merck silica gel $F_{254}$ plates and precoated Macherey–Nagel (Düren, Germany) silica gel $F_{254}$ plates were used for TLC, and spots were examined under UV light at 254 nm and revealed by a phosphomolybdic/cerium sulfate solution, iodine vapour or a dinitrophenol solution. Column chromatography was performed on ICN silica gel (63–200 μM). NMR spectra were obtained with a Varian Mercury 300 spectrometer. Chemical shifts are given in parts per million (ppm), with $\delta$

relative to the residual solvent peak ([D$_6$]DMSO: $\delta$ = 2.54 ppm for $^1$H and $\delta$ = 40.5 ppm for $^{13}$C, $CDCl_3$: $\delta$ = 7.26 ppm for $^1$H and $\delta$ = 77.4 ppm for $^{13}$C and [D$_6$]acetone: $\delta$ = 2.05 ppm for $^1$H and $\delta$ = 29.84 and 206.26 ppm for $^{13}$C). Coupling constants are expressed in Hz. Abbreviations used are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All signals assigned to hydroxy and to amino groups were exchangeable with $D_2O$. Structural assignment was confirmed with COSY, DEPT, HMQC and/or NOEDIF/NOESY if necessary. Mass spectra and exact mass measurements were performed with a quadrupole/orthogonal-acceleration time-of-flight (Q/oaTOF) tandem mass spectrometer (qTof 2, Micromass, Manchester, U. K.) equipped with a standard electrospray ionization (ESI) interface. Samples were infused in a acetonitrile/water (1:1) mixture at 3 μL/min. Most chemicals were obtained from Sigma–Aldrich or Acros Organics and were used without further purification.

**Diethyl (1-Phenylbut-3-enyl)phosphonate (6a):** To a stirred solution of **5a** (12 mL, 57.4 mmol) in dry THF (100 mL) cooled to –50 to –70 °C, was added a 1.6 M solution of *n*BuLi (39 mL, 63.2 mmol) in hexane under $N_2$. After stirring at the same temperature for 15 min, allyl bromide (5 mL, 57.4 mmol) was added; 1 h after this addition, the reaction mixture was refluxed for 2 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo, and the resulting oil was diluted with toluene (200 mL), washed with 10% $NH_4Cl$ (200 mL) and water (200 mL), dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (*n*-hexane/ethyl acetate, 8:2→7:3→6:4) yielded compound **6a** as a transparent oil (14.96 g, 97%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.06 (t, $J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 1.25 (t, $J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 2.61–2.74 (m, 1 H, allyl $CH_2$), 2.76–2.88 (m, 1 H, allyl $CH_2$), 3.05 (ddd, $J_{H,P}$ = 22.0 Hz, $J$ = 4.4, 11.1 Hz, 1 H, CHP), 3.62–3.75 (m, 1 H, $OCH_2CH_3$), 3.80–3.93 (m, 1 H, $OCH_2CH_3$), 3.95–4.09 (m, 2 H, $OCH_2CH_3$), 4.85–4.89 (m, 1 H, CH=C$H_{2,cis}$), 4.93–5.00 (m, 1 H, CH=C$H_{2,trans}$), 5.51–5.65 (m, 1 H, C$H$=$CH_2$), 7.17–7.30 (m, 5 H, arom. H) ppm.$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.46 (d, $^3J_{C,P}$ = 5.7 Hz, $OCH_2CH_3$), 16.63 (d, $^3J_{C,P}$ = 6.0 Hz, $OCH_2CH_3$), 34.26 (d, $^2J_{C,P}$ = 2.9, $CH_2CHP$), 44.81 (d, $^1J_{C,P}$ = 137.1 Hz, CHP), 62.00 (d, $^2J_{C,P}$ = 7.2 Hz, $OCH_2CH_3$), 62.77 (d, $^2J_{C,P}$ = 7.2 Hz, $OCH_2CH_3$), 117.03, 127.34, 128.62, 129.55, 135.56, 135.82 ppm. Exact mass (ESI-MS): calculated for $C_{14}H_{22}O_3P$ $[M+H]^+$ 269.1306; found 269.1292.

**General Method for the Synthesis of 8c–e:** A mixture of the appropriate acrylic aldehyde (6.17 mmol), triethyl phosphite (1.34 mL, 7.71 mmol) and phenol (1.54 g, 16 mmol) was heated to 100 °C. After 24 h, TLC analysis (hexane/ethyl acetate, 6:4) indicated that the reaction was finished, and the reaction mixture was subsequently concentrated. The crude product was purified by flash chromatography, eluting with hexane/ethyl acetate, 6:4. After concentration of the pure fractions, the desired acetals **8c**–**e** were obtained as slightly yellow oils.

**Diethyl [1-(3,4-Dichlorophenyl)-3,3-diphenoxypropyl]phosphonate (8e):** Yield: 2.29 g (70%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.13 (t, $J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 1.25 (t, $J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 2.43–2.57 (m, 1 H, $PCHCH_2$), 2.70–2.82 (m, 1 H, $PCHCH_2$), 3.38 (ddd, $J_{H,P}$ = 22.7 Hz, $J$ = 4.7, 10.3 Hz, 1 H, CHP), 3.74–3.87 (m, 1 H, $OCH_2CH_3$), 3.89–3.99 (m, 1 H, $OCH_2CH_3$), 3.99–4.12 (m, 2 H, $OCH_2CH_3$), 5.66 [dd, $J$ = 6.8, 4.4 Hz, 1 H, C$H$(OPh)$_2$], 6.84–6.92 (m, 3 H, arom. H), 6.97–7.03 (m, 2 H, arom. H), 7.18–7.27 (m, 6 H, arom. H), 7.37–7.45 (m, 2 H, arom. H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.51 (app. t, $^3J_{C,P}$ = 5.8 Hz, $OCH_2CH_3$), 34.61 (d, $^2J_{C,P}$ too small for detection, $PCHCH_2$), 39.70 (d, $^1J_{C,P}$ = 139.9 Hz, CHP), 62.57 (d, $^2J_{C,P}$ = 7.2 Hz, $OCH_2CH_3$), 63.16 (d, $^2J_{C,P}$ = 6.6 Hz, $OCH_2CH_3$), 99.34 [d, $^3J_{C,P}$ = 15.8 Hz, C$H$(OPh)$_2$], 117.66 (arom. C), 117.68 (arom. C), 122.99 (arom. C), 123.01 (arom. C), 128.75 (d, arom. C), 129.83 (arom. C), 129.85 (arom. C), 130.81 (d, arom. C), 131.29 (d, arom. C), 131.87 (d, arom. C), 133.01 (d, arom. C), 136.27 (d, arom. C), 155.95 (arom. C), 156.04 (arom. C) ppm. Exact mass (ESI-MS): calculated for $C_{25}H_{27}Cl_2O_5PNa$ $[M+Na]^+$ 531.0871; found 531.0872.

**General Method for the Synthesis of 9a,b:** To a mixture of alkene **6a** or **6b** (6.56 mmol) and 4-methylmorpholine *N*-oxide (0.92 g, 7.87 mmol) in dioxane (40 mL) was added an aqueous 1% solution of $OsO_4$ (99.1 mg, 0.39 mmol). After stirring with protection from light at room temperature overnight, the starting material was completely converted according to TLC. Sodium periodate (2.24 g, 10.5 mmol) was then added in small portions. After completion of the reaction (2 h), the mixture was diluted with ethyl acetate (100 mL), filtered through Celite, and solids were washed with ethyl acetate. The combined filtrates were washed with saturated aqueous NaCl (100 mL), dried with $MgSO_4$, and the solvents were evaporated under vacuum to yield crude **9a** or **9b**, which were used in the next step without further purification.

**General Method for Synthesis of 9c–e:** Acetals **8c**–**e** (5.0 mmol) were hydrolyzed by treatment with a mixture of water (7 mL), acetone (35 mL) and 2 N HCl (8 mL). After heating to 60–70 °C for 3–4 h, TLC analysis (ethyl acetate) confirmed that the reaction was finished. The solvents were evaporated under vacuum, and the residue was dissolved in ethyl acetate (200 mL) and transferred to a separating funnel, where it was washed twice with water (200 mL). The organic layer was dried with $MgSO_4$ and the solvents were evaporated. The residue was purified by flash chromatography using ethyl acetate as eluent to yield **9c**–**e** as transparent oils. NMR revealed, by disappearance of the CH=O signals, that **9a**–**e** are prone to oxidation upon storage when dissolved in $CDCl_3$.

**Diethyl [1-(3,4-Dichlorophenyl)-2-formylethyl]phosphonate (9e):** Yield: 1.28 g (76%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.11 (t, $J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 1.23 (t, $J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 2.95–3.20 (m, 2 H, $PCHCH_2$), 3.62 (ddd, $J_{H,P}$ = 22.7 Hz, $J$ = 4.7, 9.7 Hz, 1 H, CHP), 3.74–3.83 (m, 1 H, $OCH_2CH_3$), 3.84–3.95 (m, 1 H, $OCH_2CH_3$), 3.96–4.07 (m, 2 H, $OCH_2CH_3$), 7.12–7.40 (m, 3 H, arom. H), 9.61–9.62 (m, 1 H, HC=O) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.54 (app. t, $^3J_{C,P}$ = 6.2 Hz, $OCH_2CH_3$), 37.20 (d, $^1J_{C,P}$ = 141.9 Hz, CHP), 44.09 (d, $^2J_{C,P}$ = 2.3 Hz, $PCHCH_2$), 62.75 (d, $^2J_{C,P}$ = 7.2 Hz, $OCH_2CH_3$), 63.34 (d, $^2J_{C,P}$ = 6.9 Hz, $OCH_2CH_3$), 128.70 (d, $^3J_{C,P}$ = 6.3 Hz, arom. C$_o$), 130.75 (d, $^4J_{C,P}$ = 2.6 Hz, arom. C$_m$), 131.15 (d, $^3J_{C,P}$ = 6.9 Hz, arom. C$_o$), 131.95 (d, $^5J_{C,P}$ = 3.7 Hz, arom. C$_p$), 132.92 (d, $^4J_{C,P}$ = 2.9 Hz, arom. C$_m$), 136.03 (d, $^2J_{C,P}$ = 7.2 Hz, arom. C$_i$), 198.13 (d, $^3J_{C,P}$ = 15.0 Hz, HC=O) ppm. Exact mass (ESI-MS): calculated for $C_{13}H_{18}Cl_2O_4P$ $[M+H]^+$ 339.03204; found 339.0325.

**General Method for the Synthesis of 10a–e and 18:** A mixture of aldehydes **9a**–**e** (3.86 mmol) and *O*-benzylhydroxylamine hydrochloride (0.61 g, 3.86 mmol) in pyridine/ethanol, 1:1 (14 mL) was stirred at room temperature under nitrogen for 1.5–6 h. After the solvent was removed by evaporation, the residue was co-evaporated three times with toluene and subsequently purified by chromatography on a silica gel column (*n*-hexane/ethyl acetate, 6:4 or 6:4→1:1) to give a mixture of benzyloxyimines **10a**–**e** as transparent oils.

**Diethyl [(*E*)- and (*Z*)-3-(Benzyloxy)imino-1-(3,4-dichlorophenyl)propyl]phosphonate (10e):** Yield: 1.57 g (92%) $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.17 (dt, $J_{H,P}$ = 1.47 Hz, $J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 1.28 (dt, $J_{H,P}$ = 3.2 Hz, $J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 2.72–3.05

(m, 2 H, CHPC$H_2$), 3.17–3.32 (m, 1 H, PCH), 3.81–3.90 (m, 1 H, OC$H_2$CH$_3$), 3.93–3.98 (m, 1 H, OC$H_2$CH$_3$), 3.99–4.10 (m, 2 H, OC$H_2$CH$_3$), 4.97 (s, 1 H, OC$H_2$Ph), 5.08 (s, 1 H, OC$H_2$Ph), 6.55 (t, $J$ = 5.3 Hz, 1 H, HC=N), 7.11–7.39 (m, 8 H, arom. H) ppm. Exact mass (ESI-MS): calculated for $C_{20}H_{25}Cl_2NO_4P$ $[M+H]^+$ 444.090; found 444.091.

**Diethyl {3-[(Benzyloxy)imino]cyclopentyl}phosphonate (18):** Yield: 3.07 g (90%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.30 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$C$H_3$), 1.31 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$C$H_3$), 1.80–2.89 (m, 7 H, $C_5H_7P$), 4.04–4.15 (m, 4 H, OC$H_2$CH$_3$), 5.06 (s, 2 H, C$H_2$Ph), 7.26–7.34 (m, 5 H, arom. H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.74 (d, $^3J_{C,P}$ = 5.8 Hz, OCH$_2$CH$_3$), 25.68 (d, $J_{C,P}$ = 2.6 Hz, CH$_2$), 26.03 (d, $J_{C,P}$ = 3.2 Hz, CH$_2$), 27.92 (d, $J_{C,P}$ = 12.1 Hz, CH$_2$), 29.19 (d, $J_{C,P}$ = 1.7 Hz, CH$_2$), 30.91 (d, $J_{C,P}$ = 11.5 Hz, CH$_2$), 32.07 (d, $J_{C,P}$ = 1.4 Hz, CH$_2$), 34.77 (d, $J_{C,P}$ = 151.4 Hz, CHP), 34.99 (d, $J_{C,P}$ = 151.7 Hz, CHP), 62.06 (m, OCH$_2$CH$_3$), 75.92 (OCH$_2$Ph), 75.95 (OCH$_2$Ph), 127.93 (arom. C), 127.95 (arom. C), 128.16 (arom. C), 128.18 (arom. C), 128.56 (arom. C), 128.55 (arom. C), 138.26 (arom. C), 138.33 (arom. C), 164.12 (d, $^3J_{C,P}$ = 13.8 Hz, C=N), 164.33 (d, $^3J_{C,P}$ = 15.0 Hz, C=N) ppm. $^{31}$P NMR (120 MHz, $CDCl_3$): $\delta$ = 32.12, 32.36 ppm. Exact mass (ESI-MS): calculated for $C_{16}H_{25}NO_4P$ $[M+H]^+$ 326.1521; found 326.1523.

**General Procedure for the Reduction of the *O*-Benzyloximes 10a–e to 11a–e and 18 to 19:** Sodium cyanoborohydride (12.95 mmol, 0.81 g) was added to a solution of *O*-benzyloximes **10a**–**e** (2.59 mmol) in methanol (15 mL). Two drops of methyl orange indicator were added followed by dropwise addition of concentrated hydrochloric acid, until the solution remained pink and milky for at least 0.5 h. The reaction mixture was stirred at room temperature for 3–16 h, and the solvent was removed under vacuum. The residue was taken up in $CH_2Cl_2$ (100 mL) and washed until alkaline with 1 M potassium hydroxide solution, and the aqueous portion extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extracts were dried with $MgSO_4$, filtered and the solvent was removed. The residue was purified on a silica gel column and eluted with $CH_2Cl_2$/MeOH, 95:5 or *n*-hexane/ethyl acetate, 4:6. After concentration of the appropriate fractions, *O*-benzyloxyamines **11a**–**e** and **19** were obtained as clear oils.

**Diethyl [3-(Benzyloxyamino)-1-(3,4-dichlorophenyl)propyl]phosphonate (11e):** Yield: 1.05 g (91%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.16 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$C$H_3$), 1.28 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$C$H_3$), 1.97–2.13 (m, 1 H, C$H_2$CHP), 2.28–2.42 (m, 1 H, C$H_2$CHP), 2.64–2.74 (m, 1 H, CH$_2$N), 2.85–2.93 (m, 1 H, CH$_2$N), 3.20 (ddd, $J_{H,P}$ = 22.6 Hz, $J$ = 4.1, 11.1 Hz, 1 H, CHP), 3.77–3.89 (m, 1 H, OC$H_2$CH$_3$), 3.91–3.99 (m, 1 H, OC$H_2$CH$_3$), 3.99–4.13 (m, 2 H, OC$H_2$CH$_3$), 4.61–4.70 (m, 2 H, PhC$H_2$O), 7.13–7.17 (m, 1 H, arom. H), 7.26–7.40 (m, 7 H, arom. H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.56 (d, $^3J_{C,P}$ = 7.8 Hz, OCH$_2$CH$_3$), 16.64 (d, $^3J_{C,P}$ = 8.1 Hz, OCH$_2$CH$_3$), 27.73 (d, $^2J_{C,P}$ = 2.9 Hz, CH$_2$CHP), 41.35 (d, $^1J_{C,P}$ = 139.6 Hz, CHP), 49.48 (d, $^3J_{C,P}$ = 15.3 Hz, NCH$_2$), 62.36 (d, $^2J_{C,P}$ = 6.9 Hz, OCH$_2$CH$_3$), 62.88 (d, $^2J_{C,P}$ = 6.9 Hz, OCH$_2$CH$_3$), 77.88 (OCH$_2$Ph), 128.13 (arom. C), 128.61 (arom. C), 128.63 (arom. C), 128.87 (d, $J_{C,P}$ = 6.6 Hz, arom. C), 130.65 (d, $J_{C,P}$ = 2.6 Hz, arom. C), 131.42 (d, $J_{C,P}$ = 6.9 Hz, arom. C), 131.53 (arom. C), 132.74 (d, $J_{C,P}$ = 2.9 Hz, arom. C), 136.73 (d, $J_{C,P}$ = 6.9 Hz, arom. C), 137.88 (arom. C) ppm. Exact mass (ESI-MS): calculated for $C_{20}H_{27}Cl_2NO_4P$ $[M+H]^+$ 446.1055; found 446.1060.

**Diethyl [3-(Benzyloxyamino)cyclopentyl]phosphonate (19):** Yield: 1.83 g, mixture of *cis* and *trans* (80%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.30 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$C$H_3$), 1.30 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$C$H_3$), 1.42–2.40 (m, 8 H, $C_5H_8P$), 3.58–3.69 (m, 1 H, NH), 4.03–4.15 (m, 4 H, OC$H_2$CH$_3$), 4.69 (s, 1 H, C$H_2$Ph), 4.75 (s, 1 H, C$H_2$Ph), 7.26–7.56 (m, 5 H, arom. H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.76 (d, $^3J_{C,P}$ = 5.8 Hz, OCH$_2$CH$_3$), 25.27 (d, $J_{C,P}$ = 2.9 Hz, CH$_2$), 25.72 (d, $J_{C,P}$ = 2.6 Hz, CH$_2$), 30.18 (CH$_2$), 30.34 (CH$_2$), 31.54 (d, $J_{C,P}$ = 2.3 Hz, CH$_2$), 31.67 (d, $J_{C,P}$ = 2.1 Hz, CH$_2$), 33.73 (d, $J_{C,P}$ = 147.9 Hz, CHP), 34.55 (d, $J_{C,P}$ = 147.4 Hz, CHP), 61.65–62.13 (m, OCH$_2$CH$_3$ and NCH), 77.59 (OCH$_2$Ph), 76.95 (OCH$_2$Ph), 128.11 (arom. C), 128.61 (arom. C), 128.67 (arom. C), 129.57 (arom. C), 130.42; 137.86 (arom. C) ppm. Exact mass (ESI-MS): calculated for $C_{16}H_{27}NO_4P$ $[M+H]^+$ 328.1678; found 328.1660.

**Formylation of Compounds 11 and 19**

**Method A:** Formic acid (1 equiv.) and 2-mercaptothiazoline (1 equiv.) were dissolved in $CH_2Cl_2$ (0.5 M), cooled to 0 °C and DCC (1 equiv.) was added in one portion. After the reaction mixture was filtered and concentrated, the residue was purified by chromatography ($CH_2Cl_2$) to afford 2-thioxothiazolidine-3-carbaldehyde as a yellow solid.

**Diethyl {3-[*N*-(Benzyloxy)formamido]-1-phenylpropyl}phosphonate (12a):** 2-Thioxothiazolidine-3-carbaldehyde (1 equiv.) was dissolved in $CH_2Cl_2$ and added to a solution of **11a** (1 equiv.) in $CH_2Cl_2$ (0.1 M). The reaction mixture was stirred for 3 d. The reaction mixture was extracted with water, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5) to yield **12a** in 89% yield. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.07 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$C$H_3$), 1.26 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$C$H_3$), 2.17 (m, 1 H, C$H_2$CHP), 2.45–2.48 (m, 1 H, C$H_2$CHP), 3.06 (ddd, $J_{H,P}$ = 23.0 Hz, $J$ = 4.1, 11.1 Hz, 1 H, CHP), 3.39 (m, 1 H, CH$_2$N), 3.50 (m, 1 H, CH$_2$N), 3.62–3.75 (m, 1 H, OC$H_2$CH$_3$), 3.81–3.91 (m, 1 H, OC$H_2$CH$_3$), 3.97–4.10 (m, 2 H, OC$H_2$CH$_3$), 4.74 and 4.94 (2 × br. s, 2 H, PhC$H_2$O), 7.26–7.35 (m, 10 H, arom. H), 8.16 (br. s, 1 H, HC=O) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.40 (d, $^3J_{C,P}$ = 5.7 Hz, OCH$_2$CH$_3$), 16.58 (d, $^3J_{C,P}$ = 6.0 Hz, OCH$_2$CH$_3$), 27.42 (m, CH$_2$CHP), 40 (d, $^1J_{C,P}$ = 140 Hz, CHP), 43.11 (m, NCH$_2$), 62.19 (d, $^2J_{C,P}$ = 7.2 Hz, OCH$_2$CH$_3$), 63.96 (d, $^2J_{C,P}$ = 7.2 Hz, OCH$_2$CH$_3$), 77.42 (OCH$_2$Ph), 127.77 (arom. C), 128.91 (arom. C), 129.26 (arom. C), 129.47 (arom. C), 129.56 (arom. C), 129.63 (arom. C), 131.10 (arom. C), 135.09 (arom. C), 163.32 (m, HC=O) ppm. Mass (ESI-MS): calculated for $C_{21}H_{29}NO_5P$ $[M+H]^+$ 406.1783; found 406.1.

**Method B:** To a three-neck flask containing a solution of formic acid (0.61 mmol, 30 μL) in $CH_2Cl_2$ (0.6 mL) was added 1,1′-carbonyldiimidazole (0.64 mmol, 0.10 g). After 20 min, benzyloxyamines **11c**,**e** (0.61 mmol) were dissolved in $CH_2Cl_2$ (1 mL) and then transferred to the three-neck flask. After 5 h, the mixture was partitioned between water (70 mL) and $CH_2Cl_2$ (70 mL). The water layer was extracted twice with $CH_2Cl_2$ (70 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo, and the residue was purified by flash chromatography (*n*-pentane/acetone, 6:4) to give **12c**,**e** as transparent oils.

**Diethyl {3-[*N*-(Benzyloxy)formamido]-1-(3,4-dichlorophenyl)propyl}-phosphonate (12e):** Yield: 245 mg (85%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.14 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$C$H_3$), 1.27 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$C$H_3$), 2.07–2.21 (m, 1 H, C$H_2$CHP), 2.37–2.51 (m, 1 H, C$H_2$CHP), 3.00 (ddd, $J_{H,P}$ = 23.0 Hz, $J$ = 4.1, 11.4 Hz, 1 H, CHP), 3.23–3.38 (m, 1 H, CH$_2$N), 3.44–3.46 (m, 1 H, CH$_2$N), 3.78–3.88 (m, 1 H, OC$H_2$CH$_3$), 3.89–3.99 (m, 1 H, OC$H_2$CH$_3$), 3.99–4.11 (m, 2 H, OC$H_2$CH$_3$), 4.75 and 4.91 (2 × br. s, 2 H, PhC$H_2$O), 7.12–7.40 (m, 8 H, arom. H), 8.16 (br. s, 1 H, HC=O) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.50 (d, $^3J_{C,P}$ = 6.1 Hz, OCH$_2$CH$_3$), 16.61 (d, $^3J_{C,P}$ = 6.1 Hz, OCH$_2$CH$_3$), 27.34 (m, CH$_2$CHP), 41.46 (d, $^1J_{C,P}$ = 138.48 Hz, CHP), 42.50 (m, NCH$_2$),

62.59 (d, $^2J_{C,P}$ = 7.2 Hz, O$CH_2CH_3$), 63.09 (d, $^2J_{C,P}$ = 6.9 Hz, O$CH_2CH_3$), 78.29 (O$CH_2$Ph), 128.86 (arom. C), 128.95 (arom. C), 129.94 (arom. C), 129.69 (arom. C), 130.81 (arom. C), 131.24 (arom. C), 131.92 (arom. C), 132.93 (arom. C), 134.27 (arom. C), 135.87 (arom. C), 163.32 (m, HC=O) ppm. Exact mass (ESI-MS): calculated for $C_{21}H_{27}Cl_2NO_5P$ $[M+H]^+$ 474.1004; found 474.1000.

**Diethyl {3-[*N*-(Benzyloxy)formamido]cyclopentyl}phosphonate (20):** Yield: 1.3 g, mixture of *cis* and *trans* (97%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.23 (m, 6 H, OCH$_2$C$H_3$), 1.64–2.39 (m, 7 H, $C_5H_7$P), 3.98–4.09 (m, 4 H, OC$H_2$CH$_3$), 4.4 (m, 1 H, CHN), 4.90 (br. s, 2 H, OC$H_2$Ph), 7.30–7.32 (m, 5 H, arom. H), 8.10 and 8.13 (2 × s, 1 H, HC=O) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.76 (d, $^3J_{C,P}$ = 5.8 Hz, 2 C, OCH$_2$CH$_3$), 24.40 (d, $J_{C,P}$ = 2.0 Hz, $CH_2$), 25.60 ($CH_2$), 29.98 (d, $J_{C,P}$ = 7.8 Hz, $CH_2$), 33.31 (d, $^1J_{C,P}$ = 150.6 Hz, CHP), 33.66 (d, $^1J_{C,P}$ = 149.7 Hz, CHP), 57.73 (m, CHN), 59.03 (m, CHN), 62.01 (m, O$CH_2$CH$_3$), 79.50 (m, O$CH_2$Ph), 128.95–129.63 (3 arom. C), 134.72 (arom. C), 165.10 (m, HC=O) ppm. Exact mass (ESI-MS): calculated for $C_{17}H_{27}NO_5P$ $[M+H]^+$ 356.1627; found 356.1629.

**General Method for the Benzyl Deprotection of 12, 13, 20 and 21:** A solution of compounds **12** and **13** or **20** and **21** (0.9 mmol) in MeOH (8 mL) was hydrogenated at atmospheric pressure in the presence of Pd (10 wt.-% on activated carbon, 40 mg). After stirring for 5 h, the reaction mixture was filtered through a Celite pad. The solvent was removed under vacuum, and the crude mixture was purified by column chromatography on silica gel ($CH_2Cl_2$/MeOH, 95:5).

**Diethyl [1-(3,4-Dichlorophenyl)-3-(*N*-hydroxyformamido)propyl]-phosphonate (14e):** Yield: 157 mg (57%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.09–1.24 (m, 6 H, OCH$_2$C$H_3$), 2.11 (m, 1 H, C$H_2$CHP), 2.46 (m, 1 H, C$H_2$CHP), 3.01–3.17 (m, 1 H, CHP), 3.22–3.35 (m, 1 H, $CH_2$N), 3.45–3.56 (m, 1 H, $CH_2$N), 3.77–4.04 (m, 4 H, OC$H_2$CH$_3$), 7.08–7.11 (m, 1 H, arom. H), 7.32–7.37 (m, 2 H, arom. H), 7.55 (br. s, 1 H, HC=O), 8.24 (s, 1 H, NOH) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.48 (app. t, $^3J_{C,P}$ = 5.8 Hz, OCH$_2$CH$_3$), 26.90 (*C*H$_2$CHP, major), 27.08 (*C*H$_2$CHP, minor), 40.09 (d, $^1J_{C,P}$ = 139.3 Hz, CHP, major), 40.96 (d, $^1J_{C,P}$ = 139.3 Hz, CHP, minor), 44.60 (d, $^3J_{C,P}$ = 15.8 Hz, $NCH_2$, minor), 47.45 (d, $^3J_{C,P}$ = 15.0 Hz, $NCH_2$, major), 62.84 (d, $^2J_{C,P}$ = 6.9 Hz, O$CH_2$CH$_3$, major), 63.01 (d, $^2J_{C,P}$ = 7.2 Hz, O$CH_2$CH$_3$, minor), 63.24 (d, $^2J_{C,P}$ = 6.9 Hz, O$CH_2$CH$_3$, major), 63.32 (d, $^2J_{C,P}$ = 6.1 Hz, O$CH_2$CH$_3$, minor), 128.81 (d, $J_{C,P}$ = 6.3 Hz, arom. C, major), 128.95 (d, $J_{C,P}$ = 6.9 Hz, arom. C, minor), 130.69 (arom. C, minor), 130.91 (arom. C, major), 131.14 (d, $J_{C,P}$ = 6.9 Hz, arom. C, major), 131.24 (d, $J_{C,P}$ = 9.2 Hz, arom. C, minor), 131.74 (d, $J_{C,P}$ = 3.8 Hz, arom. C, minor), 131.98 (d, $J_{C,P}$ = 3.8 Hz, arom. C, major), 132.70 (d, $J_{C,P}$ = 2.6 Hz, arom. C, minor), 133.01 (d, $J_{C,P}$ = 2.6 Hz, arom. C, major), 135.60 (d, $J_{C,P}$ = 7.2 Hz, arom. C, major), 136.00 (d, $J_{C,P}$ = 7.5 Hz, arom. C, minor), 157.37 (C=O, major), 163.03 (C=O, minor) ppm. Exact mass (ESI-MS): calculated for $C_{14}H_{21}Cl_2NO_5P$ $[M+H]^+$ 384.0535; found 384.0530.

**Diethyl [3-(*N*-Hydroxyformamido)cyclopentyl]phosphonate (*cis*-22):** Yield: 90 mg (19%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.26 (m, 6 H, OCH$_2$C$H_3$), 1.75–2.42 (m, 7 H, $C_5H_7$P), 4.03–4.22 (m, 4 H, OC$H_2$CH$_3$), 4.83 (s, 1 H, C*H*NOH), 7.88 (s, 1 H, HC=O), 8.25 (s, 1 H, HC=O), 9.70 (s, 1 H, NOH) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.65 (d, $^3J_{C,P}$ = 5.8 Hz, OCH$_2$CH$_3$), 26.15 ($CH_2$, major), 26.66 ($CH_2$, minor), 29.21 (d, $J_{C,P}$ = 12.7 Hz, $CH_2$, minor), 29.81 (d, $J_{C,P}$ = 11.5 Hz, $CH_2$, major), 29.81 ($CH_2$, minor), 30.44 ($CH_2$, major), 33,54 (d, $^1J_{C,P}$ = 148.3 Hz, CHP, major), 35,51 (d, $^1J_{C,P}$ = 148.9 Hz, CHP, minor), 55.08 (d, $^3J_{C,P}$ = 12.7 Hz, CHN, major), 60.19 (d, $^3J_{C,P}$ = 11.5 Hz, CHN, minor), 62.05 (O$CH_2$CH$_3$), 62.15 (O$CH_2$CH$_3$), 156.49 (C=O, major), 162.37 (C=O, minor) ppm. Exact mass (ESI-MS): calculated for $C_{10}H_{21}NO_5P$ $[M+H]^+$ 266.1158; found 266.1131.

**Diethyl [3-(*N*-Hydroxyformamido)cyclopentyl]phosphonate (*trans*-22):** Yield: 170 mg (35%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.18 (t, $J$ = 7.0 Hz, 3 H, OCH$_2$C$H_3$), 1.18 (t, $J$ = 6.8 Hz, 3 H, OCH$_2$C$H_3$), 1.75–2.08 (m, 7 H, $C_5H_7$P), 3.95 (m, 4 H, OC$H_2$CH$_3$), 4.68 (s, 1 H, C*H*NOH), 7.80 (s, 1 H, HC=O, minor), 8.17 (s, 1 H, HC=O, major), 9.78 (br. s, 1 H, NOH) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 16.60 (d, $^3J_{C,P}$ = 5.5 Hz, OCH$_2$*C*H$_3$), 25.25 ($CH_2$), 28.08 (d, $J_{C,P}$ = 10.4 Hz, $CH_2$, major), 28.83 (d, $J_{C,P}$ = 11.2 Hz, $CH_2$, minor), 29.4 (s, $CH_2$, major), 30.07 ($CH_2$, minor), 33.41 (d, $^1J_{C,P}$ = 148.3 Hz, CHP, major), 34.22 (d, $^1J_{C,P}$ = 150.0 Hz, CHP, minor), 55.44 (d, $^3J_{C,P}$ = 15.8 Hz, CHN, major), 60.50 (d, $^3J_{C,P}$ = 18.1 Hz, CHN, minor), 62.10–62.47 (m, 2C, O$CH_2$CH$_3$), 156.43 (C=O, minor), 162.48 (C=O, major) ppm. Exact mass (ESI-MS): calculated for $C_{10}H_{21}NO_5P$ $[M+H]^+$ 266.1158; found 266.1143.

**General Method for the Phosphonate Deprotection:** Esters **14**, **15**, **22** or **23** (0.84 mmol) were dissolved in $CH_2Cl_2$ (10 mL) and treated dropwise with TMSBr (3.36 mmol, 0.50 g) under $N_2$. The reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the volatile compounds were removed in vacuo to give the corresponding phosphonic acids in almost quantitative yield. All final compounds were purified using a preparative HPLC system on a C18 column (5 μm; Phenomenex; Luna; 250 × 21.2 mm) with a linear gradient of acetonitrile (0→100%) in 5 mM $NH_4$OAc solution at a flow rate of 17.5 mL/min over 20 min. The purity of all target compounds was assessed by analytical HPLC [5 μm; Phenomenex; C18(2), 250 × 4.6 mm] using the same gradient at a flow rate of 1 mL/min. All final compounds were obtained as hygroscopic powders after lyophilisation. All powders were white, except the five-membered cyclic analogues which were obtained as orange powders.

**[1-(3,4-Dichlorophenyl)-3-(*N*-hydroxyformamido)propyl]phosphonic Acid (1e):** $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 1.93–2.15 (m, 1 H, β-CH), 2.24–2.38 (m, 1 H, β-CH), 2.73–2.87 (m, 1 H, α-CH), 3.17–3.47 (m, 2 H, γ-$CH_2$), 7.07–7.12 (m, 1 H, arom. H), 7.33–7.39 (m, 2 H, arom. H), 7.44 and 8.07 (2 × s, 1 H, HC=O) ppm. $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ = 26.49 (s, β-$CH_2$), 42.82 (d, $^1J_{C,P}$ = 129.6 Hz, α-CH), 48.86 (d, $^3J_{C,P}$ = 17.0 Hz, γ-$CH_2$), 128.92 (d, $J_{C,P}$ = 5.8 Hz, arom. C), 130.04 (d, $J_{C,P}$ = 3.8 Hz, arom. C), 130.55 (d, $J_{C,P}$ = 2.6 Hz, arom. C), 130.73 (d, $J_{C,P}$ = 6.0 Hz, arom. C), 131.88 (d, $J_{C,P}$ = 3.2 Hz, arom. C), 138.80 (d, $J_{C,P}$ = 7.2 Hz, arom. C), 159.70 (C=O, major) and 163.76 (C=O, minor) ppm. $^{31}$P NMR (121 MHz, $D_2O$): $\delta$ = 21.46, 21.78 (major and minor isomers) ppm. Exact mass (ESI-MS): calculated for $C_{10}H_{11}Cl_2NO_5P$ $[M-H]^-$ 325.9751; found 325.9745.

**[(1*R*,3*R*)-3-(*N*-Hydroxyformamido)cyclopentyl]phosphonic Acid and [(1*S*,3*S*)-3-(*N*-Hydroxyformamido)cyclopentyl]phosphonic Acid (*trans*-3):** $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 1.73–2.04 (m, 7 H, α-CH and $CH_2$), 4.13 (br. s, 1 H, NCH), 7.84, 8.07 (2 × s, 1 H, major and minor HC=O) ppm. $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ = 25.55 (d, $J_{C,P}$ = 1.2 Hz, $CH_2$), 28.56 (d, $J_{C,P}$ = 10.4 Hz, $CH_2$), 31.10 (s, $CH_2$), 35.94 (d, $^1J_{C,P}$ = 141.7 Hz, α-CH), 61.46 (d, $J_{C,P}$ = 17.3 Hz, NCH), 159.23 (C=O) ppm. $^{31}$P NMR (121 MHz, $D_2O$): $\delta$ = 27.71, 27.91 (major and minor isomers) ppm. Exact mass (ESI-MS): calculated for $C_6H_{11}NO_5P$ $[M-H]^-$ 208.0374; found 208.0366.

**[(1*R*,3*S*)-3-(*N*-Hydroxyformamido)cyclopentyl]phosphonic Acid and [(1*S*,3*R*)-3-(*N*-Hydroxyformamido)cyclopentyl]phosphonic Acid (*cis*-3):** $^1$H NMR (300 MHz, $D_2O$): $\delta$ = 1.49–2.17 (m, 7 H, α-CH and $CH_2$), 4.21 (br. m, 1 H, NCH), 7.88, 8.09 (2 × s, 1 H, major and minor HC=O) ppm. $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ = 26.73 (d, $J_{C,P}$

= 1.1 Hz, $CH_2$), 29.89 (d, $J_{C,P}$ = 11.2 Hz, $CH_2$), 30.76 ($CH_2$), 36.47 (d, $^1J_{C,P}$ = 141.5 Hz, α-CH), 61.36 (d, $J_{C,P}$ = 10.9 Hz, NCH), 159.11 (C=O) ppm. $^{31}$P NMR (121 MHz, $D_2O$): $\delta$ = 27.74 ppm. Exact mass (ESI-MS): calculated for $C_6H_{11}NO_5P$ $[M-H]^-$ 208.0374; found 208.0378.

**Supporting Information** (see footnote on the first page of this article): Experimental details ($^1$H, $^{13}$C, $^{31}$P NMR, MS) for intermediates (**6b**, **7d**–**e**, **8c**–**d**, **9c**–**d**, **10a**–**d**, **11a**–**d**, **12c**, **13a**–**e**, **14c**, **15a**–**e**, **17**, **21**, *trans*-**23**, *cis*-**23**) and final products (**1c**, **2a**–**e**, *trans*-**4**, *cis*-**4**).

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