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ARTICLE

Fosmidomycin Analogues with *N*-Hydroxyimidazole and *N*-Hydroxyimidazolone as Chelating Unit

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Fosmidomycin has been reported to have many biological activities as antibacterial, antimalarial, along with herbicidal agent. Its unique mode of action involves the inhibition of a key step of the non mevalonate pathway by blockade of a crucial enzyme, the 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR), whose expression is present in bacteria, plasmodium parasite and higher plants, but not in mammals. Herein we report the development of fosmidomycin and of FR-900098 constrained analogues belonging to an unusual heterocyclic based complexing subunit involving *N*-hydroxyimidazoles and cyclic *N*-hydroxyureas.

Introduction

During the late 1970s, fosmidomycin **1a** also known under the acronym FR-31564 was isolated from *Streptomyces lavendulae* and first evaluated as a natural antibiotic in an early phase II study for the management of bacterial infections.¹ In an *in vitro* assay with the purified recombinant *E. coli* DXR, Seto *et al.* showed that a crucial enzyme of the initial step of the mevalonate-independent pathway of isoprenoid biosynthesis,² 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR), was inhibited by fosmidomycin in a dose-dependent manner with an IC₅₀ value of 8.2 nM.³ Later, the natural antibiotic **1a** and its methyl derivative FR-900098 **1b** have been reported for their *in vitro* antimalarial activity against *Plasmodium falciparum* and *in vivo* in mice against *Plasmodium vinckei*.⁴ The efficiency of both compounds against *Plasmodium falciparum* on human has been proved after the latter cured uncomplicated malaria.⁵ Nevertheless, in human a high rate of recrudescence has been observed, which coupled to a moderate gastrointestinal absorption rate (20 to 40 % after administration of an oral dose of 7.5 mg.kg⁻¹ of **1a**) and a short half-life *per os* (~ 2 h) has probably precluded fosmidomycin as a monotherapeutic agent towards malaria.⁶ On the other hand, two other clinical trials using a combination of fosmidomycin-clindamycin gave promising results for a possible new treatment against malaria.⁷ But at the best of our knowledge, no therapy using these two compounds has been commercialized yet and this prompted the search for better effective inhibitors.⁸ This phosphonic acid antibiotic, also proved to be effective against the DXR enzyme of higher plants,⁹ and its herbicide activity has even been patented.¹⁰ The combined low mammalian toxicity (LD₅₀ rats, oral > 8 g.kg⁻¹)⁴ and high hydrophilic properties of the fosmidomycin **1a** and its acetyl analogue **1b** present a great interest to discover a novel class of compounds for herbicide applications. Consequently, both structures have been seen as valuable leads for the preparation of new inhibitors of DXR in higher plants. Due to considerable conformational rearrangement of DXR upon formation of the DXR-fosmidomycin complex, two sites are of a crucial importance for tight binding, selectivity and for the development of effective

molecules.¹¹ The positively charged pocket binds the phosphonate group of fosmidomycin with a high specificity whereas an amphipathic region binds the hydroxamic acid through complexation with a divalent cation, generally magnesium. The hydrophobic region of the carbon backbone is considered as a modulatory region and is exploited by different classes of fosmidomycin-like inhibitors. Then, modulation of the cation-complexing unit along with the modulatory region offers fine-tuning possibilities.¹²

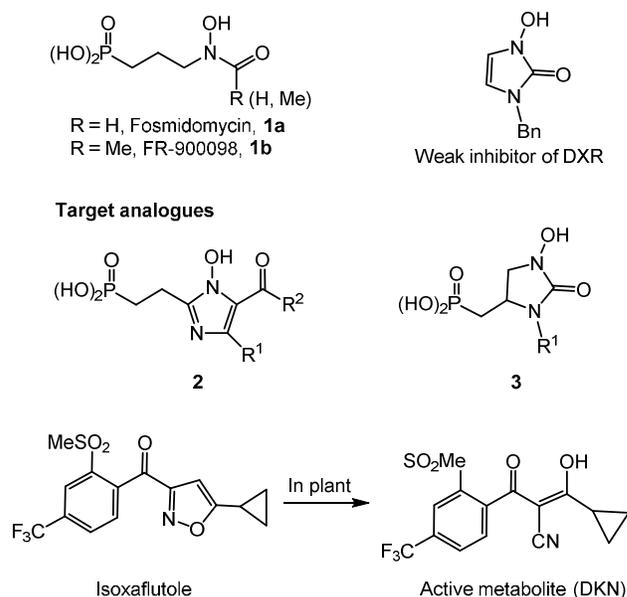


Figure 1. Fosmidomycin **1a**, FR-900098 **1b** and a weak inhibitor of DXR. Sterically strained analogues **2** and **3**. Isoxaflutole and its active metabolite (DKN).

In this context, the 5-acyl-*N*-hydroxyimidazoles **2** were perceived as molecules having a highly potent complexing unit by comparison with the parent molecules **1a-b** (Figure 1). Chelation

based on acyl-*N*-hydroxyimidazoles **2** has without ambiguity interesting features.

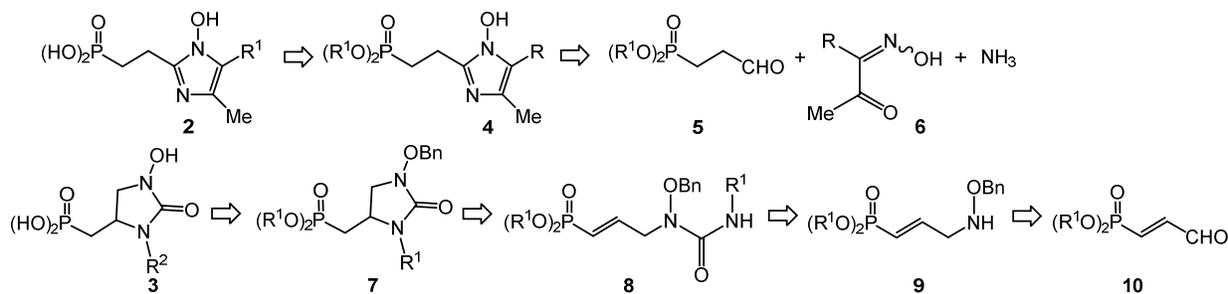


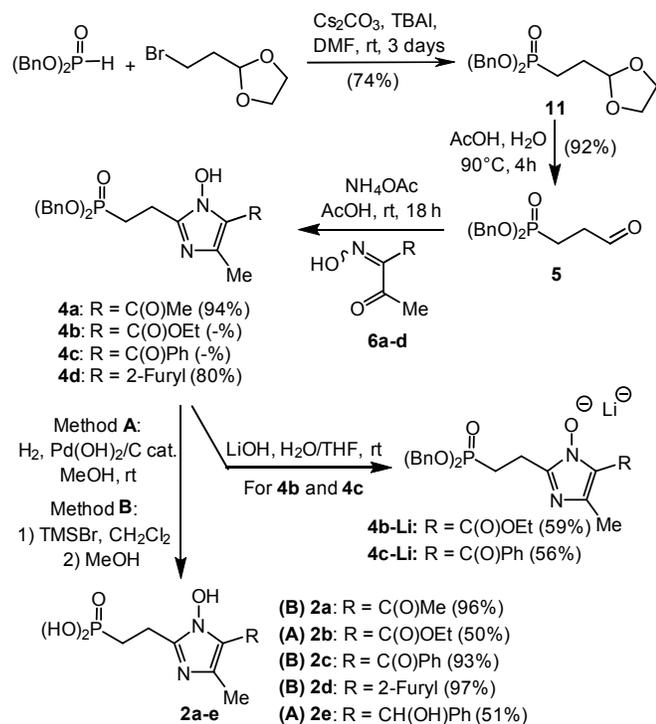
Figure 2. Retrosynthetic pathways for targeted hydroxyimidazoles **2** and hydroxyimidazolones **3**.

First of all, the complexing moiety can be seen as a close pharmacophore of the bioactive metabolite, diketone nitrile (DKN) which is referred to be an iron complexing agent and an inhibitor of the 4-hydroxyphenylpyruvate dioxygenase (HPPD), a ferrous iron metalloenzyme. DKN is generated by conversion in plants from Isoxaflutole herbicide,¹³ and the presence of a β -(1,3)-diketone moiety permits the creation of a stable ion-dipole interaction in the active enzyme active site (Figure 1). Secondly, conformational restriction due to imidazole ring, constituted another feature justifying the preparation of acyl-*N*-hydroxyimidazoles **2**. In the same way, *N*'-benzyl-*N*-hydroxyurea was already reported as a modest of DXR (Figure 1).¹⁴ Nevertheless, the targeted cyclic *N*-hydroxyureas **3** can be considered as closer and conformationally modified fosmidomycin **1a** analogues. These original structures are fully different from those previously tested and could be present interesting features for the development of new herbicides. *N*-hydroxyimidazoles **2** were obtained from the phosphonate **4**. The key step of the chemical pathway was a three-component cyclisation of substituted α -ketooximes **6**^{15,16} with the 3-phosphonopropionaldehyde **5**¹⁷ and ammonia (Figure 2). In the other side, *N*-hydroxyurea derivatives **3** were intended to be synthesized by a 5-exo-trig cyclization according to the Baldwin rules of compound **8** coming from the phosphonoallylamine **9** by reaction with an isocyanate. The *O*-benzylhydroxyamino group should be accessible from reductive oximation of the β -phosphonoacrolein **10**. The last steps of the synthesis of **3** are the cleavage of the phosphonic ester functions and a critical hydrogenolysis of the *O*-benzyl protective group without cleavage of the N-O bond.

Results and discussion

The 4-dibenzylphosphono-propionaldehyde **5** was an expected intermediate for the preparation of the *N*-hydroxyimidazolyl derivatives **2** (Scheme 1). It was accessible by adapting a two-step sequence which started from the Michaelis-Becker reaction of dibenzyl phosphite with bromoethyldioxolane promoted by caesium carbonate (Cs_2CO_3) instead of sodium hydride. The resulting dibenzyl (2-(1,3-dioxolane-2-yl)ethylidene)phosphonate **11** was obtained in 74% yield. An acidic work-up using acetic acid in water gave almost quantitatively the aldehyde **5** without hydrolysis of the phosphonic ester function. (Scheme 1).¹⁷ In parallel, substituted ketooximes **6a-d** were prepared according to the reaction of the corresponding ketone with a hydrochloric solution of sodium nitrite in 41% to 86% yields.^{15,16} The reaction of cyclisation between aldehyde **5** and α -hydroxyiminocarbonyl derivatives **6a-d** was performed in mild conditions using ammonium acetate as a source of ammonia in acetic acid at room temperature.¹⁸ The desired products **4a-d** were obtained after flash chromatography in isolated yield

ranging from 56% to 94%. Interestingly, when unsymmetrical diketone such as 2-hydroxyimino-1-phenyl-butane-1,3-dione **6c** was used, a full regioselectivity was observed, only affording the phenylketo-hydroxyimidazole **4c**. The benzyl protected phosphonic esters were not stable on storage for a long period of time giving products resulting from an internal nucleophilic substitution and forming a *N*-benzyloxyimidazolyl phosphonic acid monoester. Then reaction of **4b** and **4c** by addition of one equivalent of lithium hydroxide in a mixture water/THF (1:1) gave the stable lithium salts. An acid-base titration with a diluted aqueous solution of hydrogen chloride permitted to determine a pKa around 5.5 for these products **4b-Li** and **4c-Li**. Several catalysts were tested for the cleavage of benzyl group of phosphonate **4a-d** (Pd/C, $\text{Pd}(\text{OH})_2/\text{C}$ and Pd/BaSO_4) keeping in mind to minimize the cleavage of the sensitive N-O bond.^{19,20} The best results were observed with $\text{Pd}(\text{OH})_2/\text{C}$ in methanol at room temperature with hydrogen at 1.0 bar pressure (Scheme 2). Then, phosphonic acid **2b** was obtained after recrystallization in 50% yield. In the same conditions, the reaction on **4c** gave the alcohol **2e** in 51% yield by reduction of the ketone concomitantly with the cleavage of the benzyl group. To circumvent this side-reaction, bromo trimethylsilane has been used for **4a**, **4c** and **4d**, affording after solvolysis in methanol the desired phosphonic acids **2a**, **2c** and **2d**.



Scheme 1. Synthesis of hydroxyimidazoles **4a-d** and **2a-e**.

Slow crystallisation of the three final products into water gave single crystals which were analysed by X-ray experiments, confirming thus each structure (Figure 3).²¹ These compounds **2a-b** and **2d** existed as zwitterionic imidazoliums by protonation of

nitrogen in position 3.

The molecular packing in the single crystals showed intermolecular hydrogen bonding between the *N*-hydroxy group and an oxygen atom of the phosphonic acid group. Surprisingly, no intramolecular hydrogen bonding between the *N*-hydroxy group and heteroatom on the substituent in position 5 was highlighted. The *N*-hydroxyimidazole **2b** crystallized with one molecule of water in a P21/n crystal cell. On the contrary *N*-hydroxyimidazole **2a** and **2d** crystallized without water and presented a crystal cell with Pn and P21/n space group symmetry, respectively.

For the second series of fosmidomycin analogues **3**, the 3-phosphonoacrolein intermediate **10** was obtained from oxiranylmethylphosphonate **12** (Scheme 2). For that purpose, two different methodologies have been tested. The first one was an Arbuzov reaction between epichlorhydrin and triethyl phosphite, nevertheless the reaction revealed unsuccessful forming diethyl methylphosphonate. When using epibromohydrin, oxiranylmethyl phosphonate **12** was isolated only in a low yield (20%, litt.²² 61.9%). Therefore, another way using oxidation of commercial allylphosphonate with *m*-CPBA in dichloromethane has been preferred and furnished the expected epoxide **12** in multigram scale (Scheme 2).²³ The 3-phosphonoacrolein **10** synthesis was achieved according to a three-step sequence involving a treatment by sodium methoxide, followed by an elimination mediated by Dowex resin and subsequent oxidation of the resulting alcohol with PCC.²⁴ A reductive amination was finally performed using *O*-benzyl hydroxylamine in methanol and sodium cyanoborohydride. After flash chromatography, the phosphonoallyl benzyloxamine **9** was isolated in 50% yield. The chemical diversity was introduced at the following step, by reaction of different isocyanates affording *N*-hydroxybenzylureas **8a-d** (78-100%). A favourable 5-exo-trig intramolecular Michael addition has been led with success, using

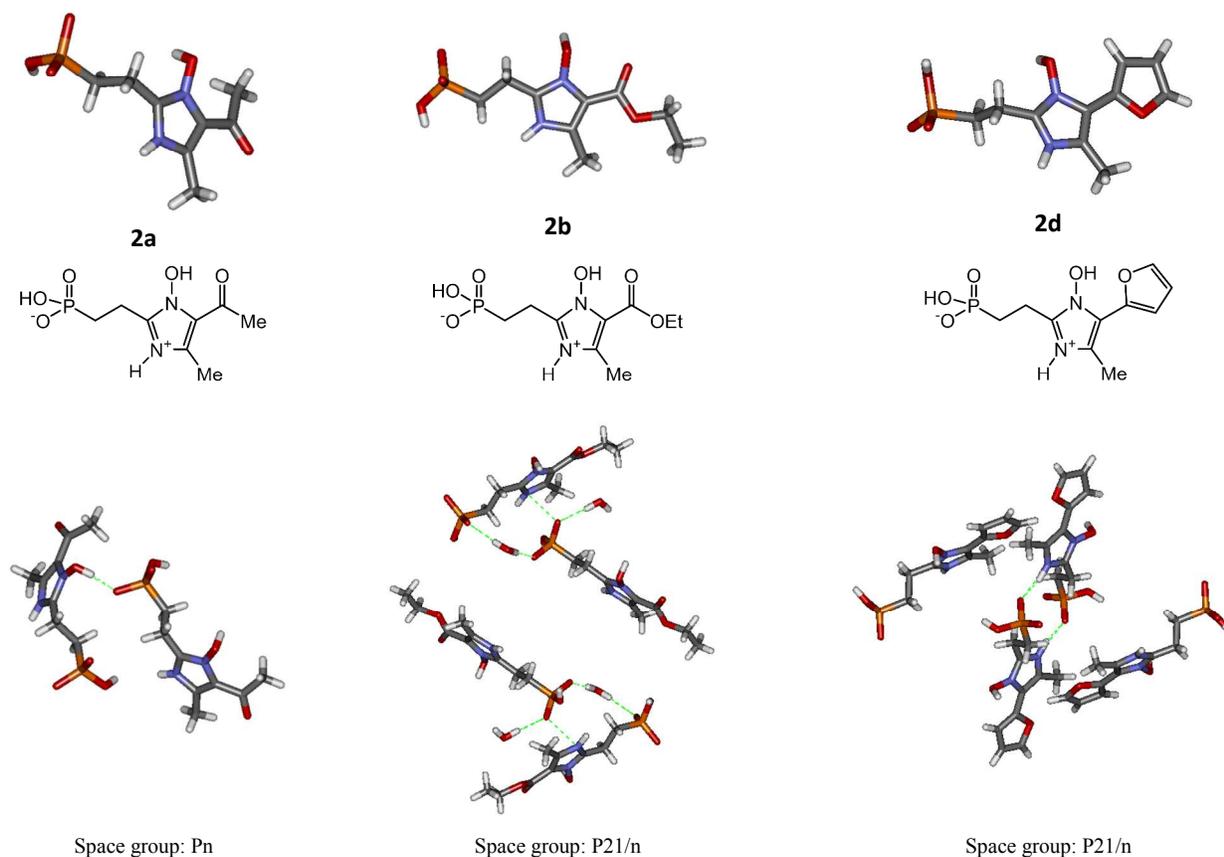
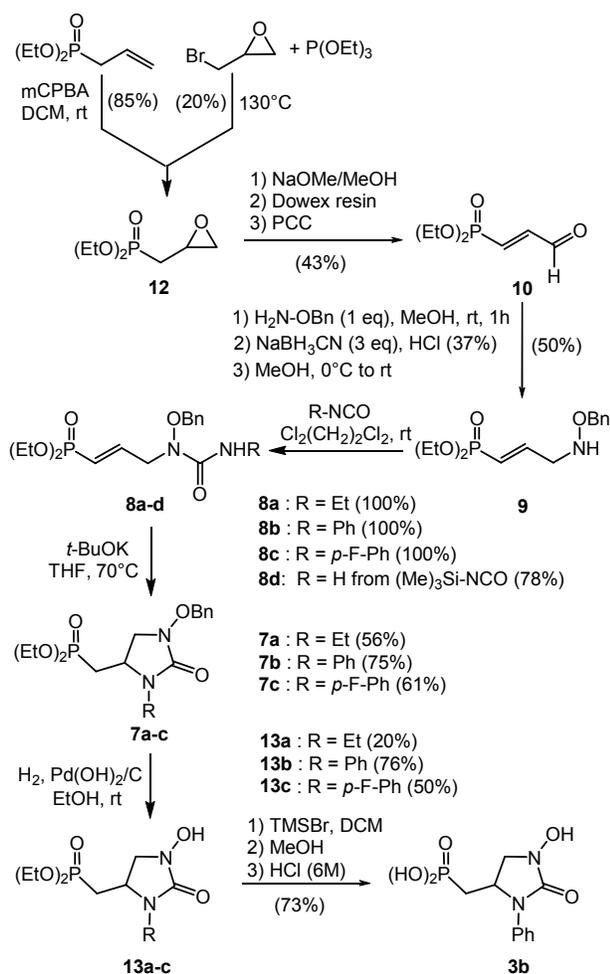


Figure 3. Conformations adopted in the crystal for phosphonic acids **2a**, **2b** and **2d** and their crystal packing.

potassium *tert*-butoxide (20 mol%) in tetrahydrofuran at 70 °C overnight. Cyclic imidazolones **7a**, **7b** and **7c** were isolated in 56 to 75% yields. For **7d** (R = H), two unidentified products were observed by ³¹P NMR with an identical ratio, but none of them was separable by column chromatography on silica or by preparative HPLC, and therefore imidazolone **7d** characterization revealed unsuccessful. The deprotection of the benzyl group of **7a-c** was first tested by hydrogenolysis with palladium hydroxide in ethanol at room temperature and overnight. For all the reactions, we observed the cleavage of the N-O bond. For phenyl **7b** and *p*-fluorophenyl **7c** derivatives, the expected imidazolones **13b-c** were obtained in 76% and 50% yields, respectively. Compound **13a** was successfully obtained by modification of the reaction conditions, using palladium hydroxide on charcoal in ethanol for only three hours. Nevertheless, only low yield (20%) of deprotected imidazolone **13a** was obtained after purification. Then, a final removal of both ethyl groups was performed on **13b** by treatment with trimethylsilyl bromide, followed by methanolysis. Nevertheless, despite a large excess of trimethylsilyl bromide (12 eq.) the reaction never reached the completion. Then a solution of hydrochloric acid (6 M) was added and the mixture was refluxed. After one night, fully deprotected phosphinic acid **3b** was obtained in 73% yield.



Scheme 2. Synthesis of protected *N*-benzoyloxyimidazolones **7a-c** and **3c**.

Experimental

General Information. All air and/or water sensitive reactions were carried out under a nitrogen atmosphere. The solvents were dried using standard methods, distilled and stored under nitrogen. Reactions were monitored by ³¹P NMR using DMSO-d₆ as internal references. Chromatography columns were performed on silica gel (Merck 60 AC, 35-70µm). All NMR spectra were recorded on a BRUKER Ultra shield 400 plus instrument at 161.99 MHz for ³¹P, 376.50 MHz for ¹⁹F, 400.13 MHz for ¹H and 100.61 MHz for ¹³C. The spectrometer used for low and high mass resolution spectra was electrospray ionization (ESI) WATERS Micromass Q-ToF spectrometer with as internal reference H₃PO₄ (0.1 % in water/acetonitrile, 1:1).

Preparation of precursor.

Dibenzyl (3-oxopropyl)phosphonate (5) was prepared in two steps from dibenzylphosphite according to the procedure already described.¹⁷ Nevertheless for the first step, cesium carbonate in the presence of iodide tetrabutylammonium has been used instead of sodium hydride.

Preparation of precursors. α -Keto oximes (6)

3-Hydroxyimino-pentane-2,4-dione (6a).^{15a-b} At -5°C, a solution of nitrite sodium (7.1 g, 0.10 mol) in water (20 mL) was added dropwise to a solution of acetyl acetone (10 g, 0.10 mol) in hydrochloric acid (50 mL, 2 M), and the mixture was allowed to stand for 20 min. The mixture was extracted with ethyl acetate (3 x 40 mL), then combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The crude was purified by recrystallization from chloroform affording the expected compound as a white solid. Yield: 86% (11.1 g).

General Procedure for 6b-d. At -10°C, a solution of nitrite sodium (1.26 g, 1.77 mmol) in water (20 mL) was added dropwise over 30 min to a solution of ketone (1.61 mmol) in acetic acid (15 mL). The mixture was allowed to stand at room temperature for 2 h. Then, the product was extracted with ethyl acetate (3 x 70 mL), combined organic layers were dried over magnesium sulfate and concentrated in vacuo. After purification, the compound was used directly in the next step because of its low stability.

Ethyl 2-(hydroxyimino)-3-oxobutanoate (6b).^{15a,15c} The purification by recrystallization from toluene afforded the expected compound. Yield: 74% (0.19 g).

2-(Hydroxyimino)-1-phenylbutane-1,3-dione (6c).¹⁶ The purification by recrystallization from toluene afforded the expected compound. Yield: 62% (0.19 g).

1-(Furan-2-yl)-2-(hydroxyimino)butane-1,3-dione (6d).¹⁶ The purification by recrystallization from toluene afforded the expected compound. Yield: 41% (0.12 g). ¹H NMR (400.13 MHz, CDCl₃) δ 2.44 (s, 3H), 6.48 (dd, ³J_{HH} = 3.1 Hz, ³J_{HH} = 1.4 Hz, 1H), 7.28 (d, ³J_{HH} = 3.1 Hz, 1H), 7.51 (d, ³J_{HH} = 1.4 Hz, 1H). ¹³C NMR (100.61 MHz, CDCl₃) δ 28.65, 112.62, 118.5, 147.31, 150.34, 156.67, 197.65, 200.39.

General Procedure. *N*-hydroxyimidazoles (**4a-d**). A solution containing dibenzyl (3-oxopropyl)phosphonate (**5**, 1.0 g, 3.15 mmol), α -keto oxime (**6a-d**, 4.7 mmol) and ammonium acetate (315 mg, 4.1 mmol) in acetic acid (50 mL) was stirred at room temperature for 12 h. Water (40 mL) was poured into the reaction mixture and the mixture was extracted with ethyl acetate (80 mL).

The combined organic layers were dried over magnesium sulfate and concentrated in vacuo.

Dibenzyl (2-(5-acetyl-1-hydroxy-1H-imidazol-2-yl)ethyl)phosphonate (4a). The resulting residue was purified by column chromatography (silica, EtOAc/EtOH (100:0 to 70:30), to afford the desired product. Yield: 94% (1.26 g). ¹H NMR (400.13 MHz, CDCl₃) δ 2.14–2.22 (m, 2H), 2.34 (s, 3H), 2.38 (s, 3H), 2.89–2.97 (m, 2H), 4.88 (dd, ²J_{HH} = 11.8 Hz, ³J_{HP} = 8.0 Hz, 2H), 4.95 (dd, ²J_{HH} = 11.8 Hz, ³J_{HP} = 8.8 Hz, 2H), 7.19–7.27 (m, 10H). ¹³C NMR (100.61 MHz, CDCl₃) δ 16.60 (s), 18.53 (d, ²J_{CP} = 3.6 Hz), 22.97 (d, ¹J_{CP} = 141.3 Hz), 28.19 (s), 67.41 (d, ²J_{CP} = 6.1 Hz), 122.27 (s), 127.87 (s), 128.47 (s), 128.61 (s), 136.04 (d, ³J_{CP} = 6.6 Hz), 141.66 (d, ³J_{CP} = 15.3 Hz), 190.88 (s). ³¹P NMR (161.97 MHz, CDCl₃) δ 31.14 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₂₆N₂O₅P 429.1579, found 429.1577.

Lithium 2-(2-(bis(benzyloxy)phosphoryl)ethyl)-5-(ethoxycarbonyl)-1H-imidazol-1-olate (4b-Li). The resulting residue was purified by column chromatography (silica, EtOAc/EtOH 100:0–70:30) to afford the *N*-hydroxyl intermediate **4b** (0.85 g, 1.85 mmol). **4b** was dissolved in tetrahydrofuran (10 mL) and a solution of lithium hydroxide monohydrate (0.078 g, 1.85 mmol) in water (5 mL) was slowly added. The resulting mixture was stirred for an additional 1 h. After concentration in vacuo, the lithium salts **4b-Li** was obtained. Yield: 59% (0.86 g). ¹H NMR (400.13 MHz, DMSO-d₆) δ 1.26 (t, ³J_{HH} = 7.0 Hz, 3H), 2.18–2.30 (m, 2H), 2.21 (s, 3H), 2.75–2.81 (m, 2H), 4.19 (q, ³J_{HH} = 7.0 Hz, 2H), 4.98 (dd, ²J_{HH} = 12.1 Hz, ³J_{HP} = 7.4 Hz, 2H), 5.03 (dd, ²J_{HH} = 12.1 Hz, ³J_{HP} = 8.3 Hz, 2H), 7.19–7.27 (m, 10H). ¹³C NMR (100.61 MHz, DMSO-d₆) δ 14.26 (s), 16.87 (s), 18.76 (d, ²J_{CP} = 2.9 Hz), 21.95 (d, ¹J_{CP} = 136.8 Hz), 59.26 (s), 66.25 (d, ²J_{CP} = 5.6 Hz), 115.42 (s), 127.60 (s), 128.04 (s), 128.40 (s), 136.71 (d, ³J_{CP} = 6.6 Hz), 138.98 (s), 141.18 (d, ³J_{CP} = 19.0 Hz), 163.13 (s). ³¹P NMR (161.97 MHz, DMSO-d₆) δ 32.44 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₂₇LiN₂O₆P 465.1767, found 465.1778.

Lithium 5-benzoyl-2-(2-(bis(benzyloxy)phosphoryl)ethyl)-1H-imidazol-1-olate (4c-Li). The resulting residue was purified by column chromatography (silica, EtOAc/EtOH 100:0–70:30) to afford the *N*-hydroxyl intermediate **4c** (0.87 g, 1.76 mmol). **4c** was dissolved in tetrahydrofuran (10 mL) and a solution of lithium hydroxide monohydrate (0.074 g, 1.76 mmol) in water (5 mL) was slowly added. The resulting mixture was stirred for an additional 1 h. After concentration in vacuo, the lithium salts was obtained. Yield: 56% (0.88 g). ¹H NMR (400.13 MHz, DMSO-d₆) δ (ppm) 1.69 (s, 3H), 2.28–2.36 (m, 2H), 2.86–2.93 (m, 2H), 5.06 (dd, ²J_{HH} = 12.1 Hz, ³J_{HP} = 7.5 Hz, 2H), 5.1 (dd, ²J_{HH} = 12.1 Hz, ³J_{HP} = 8.2 Hz, 2H), 7.34–7.62 (m, 15H). ¹³C NMR (100.61 MHz, DMSO-d₆) δ 17.42 (s), 18.74 (d, ²J_{CP} = 2.9 Hz), 22.68 (d, ¹J_{CP} = 138.3 Hz), 66.32 (d, ²J_{CP} = 5.8 Hz), 125.27 (s), 127.63 (s), 128.04 (s), 128.07 (s), 128.24 (s), 128.41 (s), 136.69 (d, ³J_{CP} = 6.6 Hz), 140.45 (s), 141.41 (s), 142.72 (d, ³J_{CP} = 18.3 Hz). ³¹P NMR (161.97 MHz, DMSO-d₆) δ 32.37 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₇H₂₇LiN₂O₅P 497.1818, found 497.1817.

Dibenzyl (2-(5-(furan-2-carbonyl)-1-hydroxy-1H-imidazol-2-yl)ethyl)phosphonate (4d). The resulting residue was purified by column chromatography (silica, EtOAc/EtOH (100:0–70:30) to afford the desired product. Yield: 80% (1.14 g). ¹H NMR (400.13 MHz, CDCl₃) δ 2.11–2.19 (m, 2H), 2.30 (s, 3H), 2.89–2.98 (m, 2H), 4.91 (dd, ²J_{HH} = 11.9 Hz, ³J_{HP} = 8.0 Hz, 2H), 4.96 (dd, ²J_{HH} = 11.9 Hz, ³J_{HP} = 9.3 Hz, 2H), 6.37 (dd, ³J_{HH} = 3.3 Hz, ³J_{HH} = 1.76 Hz, 1H), 6.72 (d, ³J_{HH} = 3.3 Hz, 1H), 7.19–7.27 (m, 11H). ¹³C NMR (100.61 MHz, CDCl₃) δ 13.13 (s), 17.66 (s), 23.29 (d, ¹J_{CP} = 140.5 Hz),

67.73 (d, ²J_{CP} = 6.6 Hz), 107.13 (s), 110.99 (s), 119.29 (s), 127.93 (s), 128.61 (s), 128.66 (s), 135.76 (d, ³J_{CP} = 5.8 Hz), 141.13 (s), 144.18 (s). ³¹P NMR (161.97 MHz, CDCl₃) δ 32.79 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₂₆N₂O₅P 453.1579, found: 453.1582.

Deprotection reaction. *N*-hydroxyimidazoles. Method A: In a Schlenk tube was introduced palladium dihydroxide on charcoal (10%), dibenzyl phosphonate (**4b** or **4c**) and degassed ethanol. Three vacuum (until solvent bubbling)/nitrogen, two vacuum/hydrogen were performed on the system. After vigorously stirring at room temperature for 24 h (**4b**) or 40°C for 36 h (**4c**), the reaction mixture was filtered on celite and the filtrate was concentrated in vacuo.

(2-(5-(Ethoxycarbonyl)-1-hydroxy-1H-imidazol-2-yl)ethyl)phosphonic acid (2b). From palladium dihydroxide on charcoal (65 mg), **4b** (0.65 g, 1.42 mmol) and ethanol (10 mL), the desired product was obtained. Yield: 50% (0.20 g). ¹H NMR (400.13 MHz, D₂O): δ 1.23 (t, ³J_{HH} = 7.0 Hz, 3H), 1.96–2.04 (m, 2H), 2.38 (s, 3H), 3.05–3.14 (m, 2H), 4.27 (q, ³J_{HH} = 7.0 Hz, 2H). ¹³C NMR (100.61 MHz, DMSO-d₆): δ 8.13 (s), 10.51 (s), 15.09 (d, ²J_{CP} = 3.7 Hz), 20.06 (d, ¹J_{CP} = 136.8 Hz), 59.96 (s), 115.32 (s), 132.00 (s), 140.96 (d, ³J_{CP} = 13.9 Hz), 156.08 (s). ³¹P NMR (161.97 MHz, D₂O) δ 25.67 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₉H₁₆N₂O₆P 279.0746, found: 279.0739.

(2-(1-Hydroxy-5-(hydroxy(phenyl)methyl)-1H-imidazol-2-yl)ethyl)phosphonic acid (2e). From palladium dihydroxide on charcoal (100 mg), **4c** (0.80 g, 1.68 mmol) and ethanol (30 mL), the desired product was obtained. Yield: 51% (0.27 g). ¹H NMR (400.13 MHz, D₂O) δ 1.21–1.27 (m, 1H), 1.84–1.92 (m, 2H), 2.01 (s, 3H), 2.96–3.03 (m, 2H), 6.04 (s, 1H), 7.29–7.38 (m, 5H). ¹³C NMR (100.61 MHz, D₂O) δ 9.05 (s), 17.94 (d, ²J_{CP} = 3.6 Hz), 24.38 (d, ¹J_{CP} = 134.6 Hz), 65.11 (s), 123.52 (s), 126.02 (s), 127.50 (s), 128.23 (s), 128.78 (s), 139.37 (s), 140.71 (d, ³J_{CP} = 14.6 Hz). ³¹P NMR (161.97 MHz, D₂O) δ 21.47 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₃H₁₈N₂O₅P 313.0953, found 313.0955.

Method B: At 0°C, trimethylsilylbromide (1.27 mL, 10 mmol) was added to a solution of benzyl phosphonate (**4a**, **4c** and **4d**, 1 mmol) in dichloromethane (10 mL). The reaction mixture was allowed to stand up at room temperature and stirred for 14 h. After concentration to dryness under vacuum, methanol (10 mL) was added and the resulting mixture was stirred at room temperature for 2 h, thus concentrated in vacuo. Further purification was not required.

(2-(5-Acetyl-1-hydroxy-1H-imidazol-2-yl)ethyl)phosphonic acid (2a). Yield 96% (0.24 g). ¹H NMR (400.13 MHz, D₂O) δ 2.00–2.09 (m, 2H), 2.41 (s, 3H), 2.48 (s, 3H), 3.07–3.14 (m, 2H). ¹³C NMR (100.61 MHz, D₂O) δ 11.52 (s), 17.67 (d, ²J_{CP} = 3.6 Hz), 23.17 (d, ¹J_{CP} = 137.5 Hz), 29.58 (s), 125.20 (s), 134.54 (s), 142.96 (d, ³J_{CP} = 14.6 Hz), 190.80 (s). ³¹P NMR (161.97 MHz, D₂O) δ 24.08 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₈H₁₄N₂O₅P 249.0640, found 249.0637.

(2-(5-Benzoyl-1-hydroxy-1H-imidazol-2-yl)ethyl)phosphonic acid (2c). Yield: 93% (0.29 g). ¹H NMR (400.13 MHz, DMSO-d₆) δ 1.98–2.06 (m, 2H), 2.13 (s, 3H), 2.96–3.03 (m, 2H), 7.56–7.66 (m, 2H), 7.68–7.76 (m, 1H), 7.76–7.82 (m, 2H). ¹³C NMR (100.61 MHz, DMSO-d₆) δ 14.00 (s), 18.75 (s), 24.78 (d, ¹J_{CP} = 135.4 Hz), 125.11 (s), 128.46 (s), 129.03 (s), 132.90 (s), 137.82 (s), 144.51 (d, ³J_{CP} = 15.4 Hz), 184.73 (s). ³¹P NMR (161.97 MHz, DMSO-d₆) δ 23.58 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₃H₁₆N₂O₅P 311.0797, found: 311.0797.

(2-(5-(Furan-2-carbonyl)-1-hydroxy-1H-imidazol-2-yl)ethyl)phosphonic acid (**2d**). Yield: 97% (0.25 g). ^1H NMR (400.13 MHz, D_2O) δ 1.97–2.06 (m, 2H), 2.30 (s, 3H), 3.05–3.12 (m, 2H), 6.49 (dd, $^3J_{\text{HH}} = 3.1$ Hz, $^3J_{\text{HH}} = 1.0$ Hz, 1H), 6.78 (d, $^3J_{\text{HH}} = 3.1$ Hz, 1H), 7.55 (d, $^3J_{\text{HH}} = 1.0$ Hz, 1H). ^{13}C NMR (100.61 MHz, D_2O) δ 9.57 (s), 17.71 (d, $^2J_{\text{CP}} = 3.7$ Hz), 23.61 (d, $^1J_{\text{CP}} = 136.1$ Hz), 111.04 (s), 111.39 (s), 119.29 (s), 123.32 (s), 141.23 (d, $^3J_{\text{CP}} = 14.6$ Hz), 144.10 (s), 145.38 (s). ^{31}P NMR (161.97 MHz, D_2O) δ 24.01 (s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_5\text{P}$ 273.0640, found 273.0640.

Synthesis of diethyl (oxiran-2-ylmethyl)phosphonate (12) and diethyl (E)-(3-oxoprop-1-en-1-yl)phosphonate (10). Starting materials **12**²³ and **10**²⁴ were prepared respectively according to procedure described in literature.

Diethyl (E)-(3-(benzyloxy)amino)prop-1-en-1-yl)phosphonate (9). (E)-diethyl (3-oxoprop-1-en-1-yl)phosphonate (15.2 g, 78.2 mmol, 1 eq) was dissolved in MeOH (25 mL) and *O*-benzyl hydroxylamine (8.19 mL, 78.2 mmol, 1 eq) was added at 0°C. The mixture was stirred for 1 h at room temperature. After addition of MeOH (300 mL), NaBH_3CN (14.8 g, 230 mmol, 3 eq) was added by small portions. After 30 min at room temperature, concentrated HCl (46 mL, 37%) was added slowly at 0°C. Then, a new portion of NaBH_3CN (3.5 g, 54 mmol) was added at room temperature and one more time after 2 hours (7.0 g, 109 mmol). The reaction was stirred overnight and then concentrated under reduced pressure. An aqueous solution of KOH (10%) was added until pH = 10 and then the product was extracted three times with CH_2Cl_2 (100 mL). Organic layers were combined, dried over MgSO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (silica heptane/AcOEt 60:40–0:100) to afford the desired product. Yield: 50% (11.8 g). ^1H NMR (400.13 MHz, CDCl_3) δ 1.34 (t, $^3J_{\text{HH}} = 7.1$ Hz, 6H), 3.68–3.71 (m, 2H), 4.06–4.14 (m, 4H), 4.73 (s, 2H), 5.85–5.96 (ddt, $^2J_{\text{PH}} = 20.3$ Hz, $^3J_{\text{HH}} = 17.2$ Hz, $^4J_{\text{HH}} = 3.2$ Hz, 1H), 6.77–6.89 (ddt, $^2J_{\text{PH}} = 27.8$ Hz, $^3J_{\text{HH}} = 17.4$ Hz, $^3J_{\text{HH}} = 5.5$ Hz, 1H), 7.33–7.37 (m, 5H). ^{13}C NMR (100.61 MHz, CDCl_3) δ 16.36 (d, $^3J_{\text{CP}} = 6.4$ Hz), 54.21 (d, $^3J_{\text{CP}} = 23.2$ Hz), 61.77 (d, $^2J_{\text{CP}} = 5.6$ Hz), 77.33 (s), 119.11 (d, $^1J_{\text{CP}} = 187.8$ Hz), 127.96 (s), 128.42 (s), 137.53 (s), 148.55 (d, $^2J_{\text{CP}} = 4.9$ Hz). ^{31}P NMR (161.97 MHz, CDCl_3) δ 17.84 (s).

General Procedure. *N*-hydroxybenzylureas. Under N_2 , compound **9** (1.5g, 5 mmol) was dissolved in dichloroethane (25 mL) and isocyanate (2, 3 or 6 eq) was added. The reaction mixture was stirred at room temperature for 3 h (overnight for **8 d**). The solution was concentrated in vacuo and the resulting crude was used for the next step without further purification.

(E)-Diethyl (3-(1-(benzyloxy)-3-ethylureido)prop-1-en-1-yl)phosphonate (8a). From ethylisocyanate (1.2 mL, 15 mmol), the desired product was obtained. Yield: 100% (1.8 g). ^1H NMR (400.13 MHz, CDCl_3) δ 1.03 (t, $^3J_{\text{HH}} = 7.3$ Hz, 6H), 1.33 (t, $^3J_{\text{HH}} = 7.2$ Hz, 3H), 3.15–3.22 (m, 2H), 4.05–4.12 (m, 4H), 4.23–4.25 (m, 2H), 4.80 (s, 2H), 5.68 (t, $^3J_{\text{HH}} = 5.5$ Hz, 1H), 5.87 (ddt, $^2J_{\text{PH}} = 19.6$ Hz, $^3J_{\text{HH}} = 17.2$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, 1H), 6.72–6.84 (m, 1H), 7.36–7.41 (m, 5H). ^{13}C NMR (100.61 MHz, CDCl_3) δ 15.07 (s), 16.33 (d, $^3J_{\text{CP}} = 6.4$ Hz), 34.94 (s), 54.22 (d, $^3J_{\text{CP}} = 24.5$ Hz), 61.80 (d, $^2J_{\text{CP}} = 5.6$ Hz), 77.41 (s), 120.21 (d, $^1J_{\text{CP}} = 186.9$ Hz), 128.79 (s), 129.01 (s), 129.31 (s), 135.14 (s), 146.89 (d, $^2J_{\text{CP}} = 5.0$ Hz), 159.62 (s). ^{31}P NMR (161.97 MHz, CDCl_3) δ 17.24 (s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{28}\text{N}_2\text{O}_5\text{P}$ 371.1740, found: 371.1736.

(E)-Diethyl (3-(1-(benzyloxy)-3-phenylureido)prop-1-en-1-yl)phosphonate (8b). From phenylisocyanate (1.0 mL, 10 mmol), the

desired product was obtained. Yield: 100% (2.1 g). ^1H NMR (400.13 MHz, CDCl_3) δ 1.32 (t, $^3J_{\text{HH}} = 7.0$ Hz, 6H), 4.05–4.12 (m, 4H), 4.33–4.35 (m, 2H), 4.91 (s, 2H), 5.88–5.97 (m, 1H), 6.76–6.89 (m, 1H), 7.26–7.31 (m, 5H), 7.41–7.47 (m, 5H), 7.60 (s, 1H). ^{13}C NMR (100.61 MHz, CDCl_3) δ 16.33 (d, $^3J_{\text{CP}} = 6.6$ Hz), 51.72 (d, $^3J_{\text{CP}} = 24.9$ Hz), 61.87 (d, $^2J_{\text{CP}} = 5.9$ Hz), 77.95 (s), 119.31 (s), 120.70 (d, $^1J_{\text{CP}} = 186.6$ Hz), 123.74 (s), 128.93 (s), 129.02 (s), 129.37 (s), 129.44 (s), 134.71 (s), 137.53 (s), 146.22 (d, $^2J_{\text{CP}} = 5.1$ Hz), 156.68 (s). ^{31}P NMR (161.97 MHz, CDCl_3) δ 16.99 (s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_5\text{P}$ 419.1736, found 419.1736.

(E)-Diethyl (3-(1-(benzyloxy)-3-(4-fluorophenyl)ureido)prop-1-en-1-yl)phosphonate (8c). From 4-fluorophenylisocyanate (1.2 mL, 10 mmol), the desired product was obtained. Yield: 100% (2.1 g). ^1H NMR (400.13 MHz, CDCl_3) δ 1.32 (t, $^3J_{\text{HH}} = 7.0$ Hz, 6H), 4.05–4.13 (m, 4H), 4.32–4.35 (m, 2H), 4.90 (s, 2H), 5.88–5.97 (m, 1H), 6.76–6.88 (ddt, m, 1H), 6.95–7.01 (m, 2H), 7.20–7.23 (m, 2H), 7.35–7.44 (m, 5H), 7.51 (s, 1H). ^{13}C NMR (100.61 MHz, CDCl_3) δ 16.32 (d, $^3J_{\text{CP}} = 5.8$ Hz), 51.67 (d, $^3J_{\text{CP}} = 24.9$ Hz), 61.96 (d, $^2J_{\text{CP}} = 5.9$ Hz), 77.88 (s), 115.51 (d, $^2J_{\text{CF}} = 22.7$ Hz), 120.54 (d, $^1J_{\text{CP}} = 187.4$ Hz), 121.18 (d, $^3J_{\text{CF}} = 7.3$ Hz), 129.03 (s), 129.40 (s), 129.47 (s), 133.46 (d, $^4J_{\text{CF}} = 2.2$ Hz), 134.71 (s), 146.27 (d, $^2J_{\text{CP}} = 5.1$ Hz), 156.82 (s), 159.15 (d, $^1J_{\text{CF}} = 243.0$ Hz). ^{31}P NMR (161.97 MHz, CDCl_3) δ 17.02 (s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{27}\text{FN}_2\text{O}_5\text{P}$ 437.1642, found 437.1642.

(E)-Diethyl (3-(1-(benzyloxy)-3-ureido)prop-1-en-1-yl)phosphonate (8d). From trimethylsilyl isocyanate (4 mL, 30 mmol), followed by a column chromatography (silica), the desired product was obtained. Yield: 78% (1.3 g). ^1H NMR (400.13 MHz, CDCl_3) δ 1.31 (t, $^3J_{\text{HH}} = 7.0$ Hz, 6H), 4.03–4.10 (m, 4H), 4.22–4.23 (m, 2H), 4.83 (s, 2H), 5.49 (bs, 2H), 5.81–5.90 (m, 1H), 6.68–6.80 (m, 1H), 7.36–7.28 (m, 5H). ^{13}C NMR (100.61 MHz, CDCl_3) δ 16.35 (d, $^3J_{\text{CP}} = 6.6$ Hz), 51.21 (d, $^3J_{\text{CP}} = 24.9$ Hz), 61.85 (d, $^2J_{\text{CP}} = 5.9$ Hz), 77.42 (s), 120.25 (d, $^1J_{\text{CP}} = 187.3$ Hz), 128.82 (s), 129.10 (s), 129.25 (s), 134.73 (s), 146.31 (d, $^2J_{\text{CP}} = 5.1$ Hz), 160.21 (s). ^{31}P NMR (161.97 MHz, CDCl_3) δ 17.17 (s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_5\text{P}$ 343.1417, found 343.1423.

General Procedure. *N*-benzyloxymidazolones. Under N_2 , **8a-c** (1 eq) was dissolved in THF (0.1 mol/L) and *t*-BuOK (20 mol %) was introduced. The reaction was heated at reflux for 48 h and the mixture was concentrated under reduced pressure. Water (10 mL) was added and extracted with EtOAc (3 \times 25 mL), organic layers were combined, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica, heptane/AcOEt 50:50–0:100).

(±)-Diethyl ((1-(benzyloxy)-3-ethyl-2-oxoimidazolidin-4-yl)methyl)phosphonate (7a). From **8a** (1.2 g, 3.24 mmol), the desired product was obtained. Yield: 56% (0.67 g). ^1H NMR (400.13 MHz, CDCl_3) δ 1.12 (t, $^3J_{\text{HH}} = 7.2$ Hz, 3H), 1.32 (t, $^3J_{\text{HH}} = 7.1$ Hz, 3H), 1.33 (t, $^3J_{\text{HH}} = 7.1$ Hz, 3H), 1.79 (ddd, $^2J_{\text{HP}} = 17.1$ Hz, $^2J_{\text{HH}} = 14.8$ Hz, $^3J_{\text{HH}} = 10.7$ Hz, 1H), 2.19 (ddd, $^2J_{\text{HP}} = 21.5$ Hz, $^2J_{\text{HH}} = 15.0$ Hz, $^3J_{\text{HH}} = 2.9$ Hz, 1H), 3.02 (dq, $^2J_{\text{HH}} = 14.2$ Hz, $^3J_{\text{HH}} = 7.0$ Hz, 1H), 3.14 (dd, $^2J_{\text{HH}} = 8.2$ Hz, $^3J_{\text{HH}} = 6.6$ Hz, 1H), 3.46–3.50 (m, 1H), 3.56 (dq, $^2J_{\text{HH}} = 14.7$ Hz, $^3J_{\text{HH}} = 7.3$ Hz, 1H), 3.71–3.78 (m, 1H), 4.04–4.14 (m, 4H), 4.97 (d, $^2J_{\text{HH}} = 11.4$ Hz, 1H), 5.02 (d, $^2J_{\text{HH}} = 11.4$ Hz, 1H), 7.33–7.46 (m, 5H). ^{13}C NMR (100.61 MHz, CDCl_3) δ 12.55 (s), 16.38 (d, $^3J_{\text{CP}} = 5.9$ Hz), 16.44 (d, $^3J_{\text{CP}} = 5.9$ Hz), 28.66 (d, $^1J_{\text{CP}} = 138.8$ Hz), 35.81 (s), 46.73 (s), 53.57 (d, $^3J_{\text{CP}} = 1.4$ Hz), 61.95 (d, $^2J_{\text{CP}} = 6.6$ Hz), 62.06 (d, $^2J_{\text{CP}} = 6.6$ Hz), 77.88 (s), 128.23 (s), 128.36 (s), 129.08 (s), 136.72 (s), 162.04 (s). ^{31}P NMR (161.97 MHz, CDCl_3) δ 26.10 (s). HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{28}\text{N}_2\text{O}_5\text{P}$ 371.1736, found 371.1736.

(±)-Diethyl ((1-(benzyloxy)-3-phenyl-2-oxoimidazolidin-4-yl)methyl)phosphonate (**7b**). From **8b** (1.5 g, 3.6 mmol), the desired product was obtained. Yield: 75% (1.13 g). ¹H NMR (400.13 MHz, CDCl₃) δ 1.31 (t, ³J_{HH} = 7.0 Hz, 3H), 1.32 (t, ³J_{HH} = 7.0 Hz, 3H), 1.85 (ddd, ²J_{HP} = 16.7 Hz, ²J_{HH} = 15.2 Hz, ³J_{HH} = 11.1 Hz, 1H), 2.25 (ddd, ²J_{HP} = 21.1 Hz, ²J_{HH} = 15.2 Hz, ³J_{HH} = 2.0 Hz, 1H), 3.36 (dd, ²J_{HH} = 8.2 Hz, ³J_{HH} = 5.3 Hz, 1H), 3.63–3.67 (m, 1H), 4.03–4.15 (m, 4H), 4.36–4.44 (m, 1H), 5.05 (s, 2H), 7.17–7.20 (m, 5H), 7.36–7.50 (m, 5H). ¹³C NMR (100.61 MHz, CDCl₃) δ 16.39 (d, ³J_{CP} = 5.9 Hz), 28.48 (d, ¹J_{CP} = 138.3 Hz), 48.05 (d, ²J_{CP} = 1.5 Hz), 52.62 (s), 61.01 (d, ²J_{CP} = 6.6 Hz), 62.06 (d, ²J_{CP} = 6.6 Hz), 77.98 (s), 121.33 (s), 125.02 (s), 128.41 (s), 128.43 (s), 129.22 (s), 129.26 (s), 136.41 (s), 136.73 (s), 159.84 (s). ³¹P NMR (161.97 MHz, CDCl₃) δ 26.06 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₁H₂₈N₂O₅P 419.1724, found 419.1736.

(±)-Diethyl ((1-(benzyloxy)-3-(4-fluorophenyl)-2-oxoimidazolidin-4-yl)methyl)phosphonate (**7c**). From **8c** (1.6 g, 3.6 mmol), the desired product was obtained. Yield: 61% (0.97 g). ¹H NMR (400.13 MHz, CDCl₃) δ 1.31 (t, ³J_{HH} = 7.0 Hz, 6H), 1.82 (ddd, ²J_{HP} = 16.9 Hz, ²J_{HH} = 15.2 Hz, ³J_{HH} = 11.1 Hz, 1H), 2.18 (ddd, ²J_{HP} = 17.2 Hz, ²J_{HH} = 15.2 Hz, ³J_{HH} = 2.1 Hz, 1H), 3.34 (dd, ²J_{HH} = 8.2 Hz, ³J_{HH} = 5.8 Hz, 1H), 3.64–3.68 (m, 1H), 4.04–4.12 (m, 4H), 4.29–4.36 (m, 1H), 5.04 (s, 2H), 7.08–7.12 (m, 2H), 7.36–7.49 (m, 7H). ¹³C NMR (100.61 MHz, CDCl₃) δ 16.40 (d, ³J_{CP} = 6.0 Hz), 28.54 (d, ¹J_{CP} = 138.9 Hz), 48.43 (d, ²J_{CP} = 1.5 Hz), 52.72 (s), 62.02 (d, ²J_{CP} = 6.6 Hz), 62.12 (d, ²J_{CP} = 6.6 Hz), 78.03 (s), 116.11 (d, ²J_{CF} = 22.7), 123.53 (d, ³J_{CF} = 8.0 Hz), 128.45 (s), 129.24 (s), 132.68 (s), 136.35 (s), 159.94 (s), 160.05 (d, ¹J_{CF} = 245.9 Hz). ³¹P NMR (161.97 MHz, CDCl₃) δ 25.83 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₁H₂₇FN₂O₅P 437.1649, found 419.1642.

General Procedure. *N*-Hydroxyimidazolones. In a schlenk tube and under N₂, the appropriate amount of Pd(OH)₂/C (10%) was introduced and two vacuum-nitrogen sequences were performed. Then, the 5-membered ring derivative (1 eq) in EtOH was added and the mixture was then let under hydrogen atmosphere overnight at room temperature (3h for **7a**). The mixture was then filtered through a celite pad, and ethanol was removed under vacuum. The resulting crude was purified by column chromatography (silica, heptane/AcOEt/EtOH 90:18:2–0:90:10).

(±)-Diethyl ((1-hydroxy-3-ethyl-2-oxoimidazolidin-4-yl)methyl)phosphonate (**13a**). From **7a** (0.07 g, 0.19 mmol) and Pd(OH)₂/C (10%, 0.007 mg) in ethanol (2.5 mL), the desired product was obtained. Yield 20% (0.01 g). ¹H NMR (400.13 MHz, CDCl₃) δ 1.12 (t, ³J_{HH} = 7.1 Hz, 3H), 1.36 (t, ³J_{HH} = 7.0 Hz, 3H), 1.90 (ddd, ²J_{HP} = 17.4 Hz, ²J_{HH} = 15.0 Hz, ³J_{HH} = 10.7 Hz, 1H), 2.25 (ddd, ²J_{HP} = 21.3 Hz, ²J_{HH} = 14.8 Hz, ³J_{HH} = 2.7 Hz, 1H), 3.05 (dq, ²J_{HH} = 14.2 Hz, ³J_{HH} = 7.1 Hz, 1H), 3.34 (dd, ²J_{HH} = 8.2 Hz, ³J_{HH} = 6.6 Hz, 1H), 3.49–3.58 (m, 1H), 3.73–3.77 (m, 1H), 3.82–3.88 (m, 1H), 4.11–4.16 (m, 4H), 8.46 (bs, 1H). ¹³C NMR (100.61 MHz, CDCl₃) δ 12.59 (s), 16.44 (d, ³J_{CP} = 5.9 Hz), 16.46 (d, ³J_{CP} = 5.9 Hz), 28.70 (d, ¹J_{CP} = 139.1 Hz), 36.12 (s), 47.00 (s), 54.28 (d, ⁴J_{CP} = 1.5 Hz), 62.10 (d, ²J_{CP} = 6.6 Hz), 62.24 (d, ²J_{CP} = 6.6 Hz), 163.96 (s). ³¹P NMR (161.97 MHz, CDCl₃) δ 26.15 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₀H₂₂N₂O₅P 281.1266, found 281.1257.

(±)-Diethyl ((1-hydroxy-3-phenyl)-2-oxoimidazolidin-4-yl)methyl)phosphonate (**13b**). From **7b** (1.1 g, 2.6 mmol) and Pd(OH)₂/C (10%, 0.11 g) in ethanol (30 mL), the desired product was obtained. Yield 76% (0.66 g). ¹H NMR (400.13 MHz, CDCl₃) δ 1.35 (t, ³J_{HH} = 7.0 Hz, 3H), 1.36 (t, ³J_{HH} = 7.1 Hz, 3H), 1.95 (ddd, ²J_{HP} = 17.1 Hz, ²J_{HH} = 15.2 Hz, ³J_{HH} = 11.1 Hz, 1H), 2.28 (ddd, ²J_{HP} = 21.2 Hz, ²J_{HH} = 15.0 Hz, ³J_{HH} = 2.2 Hz, 1H), 3.61 (dd, ²J_{HH} = 8.4

Hz, ³J_{HH} = 5.8 Hz, 1H), 3.88–3.92 (m, 1H), 4.08–4.20 (m, 4H), 4.46–4.55 (m, 1H), 7.19–7.24 (m, 1H), 7.39–7.44 (m, 4H). ¹³C NMR (100.61 MHz, CDCl₃) δ 16.40 (d, ³J_{CP} = 6.6 Hz), 28.52 (d, ¹J_{CP} = 139.0 Hz), 48.34 (s), 53.44 (s), 62.24 (d, ²J_{CP} = 6.6 Hz), 62.25 (d, ²J_{CP} = 6.6 Hz), 121.90 (s), 125.31 (s), 129.30 (s), 136.60 (s), 161.93 (s). ³¹P NMR (161.97 MHz, CDCl₃) δ 26.12 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₄H₂₂N₂O₅P 329.1272, found 329.1266.

(±)-Diethyl ((1-hydroxy-3-(4-fluorophenyl)-2-oxoimidazolidin-4-yl)methyl)phosphonate (**13c**). From **7c** (0.15 g, 0.35 mmol) and Pd(OH)₂/C (10%, 0.015 g) in ethanol (4 mL), the desired product was obtained. Yield 50% (0.06 g). ¹H NMR (400.13 MHz, CDCl₃) δ 1.32 (t, ³J_{HH} = 7.0 Hz, 3H), 1.33 (t, ³J_{HH} = 7.0 Hz, 3H), 1.92 (ddd, ²J_{HP} = 17.2 Hz, ²J_{HH} = 15.2 Hz, ³J_{HH} = 11.1 Hz, 1H), 2.21 (ddd, ²J_{HP} = 17.4 Hz, ²J_{HH} = 15.0 Hz, ³J_{HH} = 2.2 Hz, 1H), 3.54 (dd, ²J_{HH} = 8.5 Hz, ³J_{HH} = 6.5 Hz, 1H), 3.87–3.91 (m, 1H), 4.04–4.17 (m, 4H), 4.37–4.46 (m, 1H), 7.06–7.10 (m, 2H), 7.32–7.37 (m, 2H). ¹³C NMR (100.61 MHz, CDCl₃) δ 16.40 (d, ³J_{CP} = 5.8 Hz), 28.60 (d, ¹J_{CP} = 139.1 Hz), 48.77 (s), 53.47 (s), 62.27 (d, ²J_{CP} = 6.6 Hz), 62.36 (d, ²J_{CP} = 6.6 Hz), 116.18 (d, ²J_{HF} = 22.7), 124.18 (d, ³J_{HF} = 8.8 Hz), 132.51 (d, ⁴J_{HF} = 2.9 Hz), 161.98 (s), 160.25 (d, ¹J_{CF} = 245.2 Hz). ³¹P NMR (161.97 MHz, CDCl₃) δ 26.06 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₄H₂₁FN₂O₅P 347.1180, found 347.1172.

(±)-(*l*-hydroxy-3-phenyl-2-oxoimidazolidin-4-yl)methylphosphonic acid (**3b**). At 0°C and under nitrogen, trimethylsilylbromide (0.47 mL, 3.65 mmol, 6 eq) was added to a solution of **13b** (200 mg, 0.61 mmol) in dichloromethane (10 mL). The reaction was stirred at room temperature overnight and concentrated in vacuum to dryness. Then, methanol was added (10 mL) and the mixture was stirred at room temperature for one hour, and then solvent was evaporated. The crude was diluted in a hydrochloride solution (6 M) and the mixture was heated at reflux for 4 hours. After evaporation, the pure product was obtained without further purification. Yield: 73% (0.12 g). ¹H NMR (400.13 MHz, D₂O) δ 1.69–1.91 (m, 2H), 3.26–3.30 (m, 1H), 3.64–3.68 (m, 1H), 4.15–4.24 (m, 1H), 7.04–7.09 (m, 3H), 7.18–7.22 (m, 2H). ¹³C NMR (100.61 MHz, D₂O) δ 28.93 (d, ¹J_{CP} = 133.9 Hz), 49.63 (d, ²J_{CP} = 1.5 Hz), 53.52 (s), 124.64 (s), 127.07 (s), 129.48 (s), 135.36 (s), 162.64 (s). ³¹P NMR (161.97 MHz, D₂O) δ 24.25 (s). HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₀H₁₄N₂O₅P 273.0639, found: 273.0640.

Conclusions

N-Hydroxyimidazoles **2a-d** and cyclic *N*-hydroxyureas **13a-c**, both rigidified analogues of fosmidomycin have been successfully prepared as potential inhibitors of DXR. Compounds **2a-d** have been prepared by a three-component reaction through the condensation-cyclization sequence between dibenzyl (3-oxopropyl)phosphonate **5**, α-ketooximes **6** and ammonium acetate. The five-membered ring hydroxyureas derivatives have been synthesized from an unusual intramolecular Michael addition leading to the desired structures. In vivo evaluations as herbicides for compounds **4a-d**, **2a-e**, **13a-c** and **3c** were conducted by spraying on different cultures of interest belonging to monocotyledons or dicotyledons. Unfortunately, no biological activity was seen in this preliminary screening. Nevertheless other *N*-hydroxyurea analogues are expected and will be evaluated in due course.

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- (a) H. P. Kuemmerle, T. Murakawa, H. Sakamoto, N. Sato, T. Konishi and F. De Santis, *Int. J. Clin. Pharmacol. Ther. Toxicol.*, 1985, **23**, 521. For review on Isoprenoid metabolism see: (b) J. de Ruyck, J. Wouters and C. D. Poulter, *Curr. Enzyme Inhib.*, 2011, **7**, 79. (c) C. Obiol-Pardo, J. Rubio-Martinez and S. Imperial, *Curr. Med. Chem.*, 2011, **18**, 1325. (d) A. J. Wiemer, C.-H. Hsiao and D. F. Wiemer, *Curr. Top. Med. Chem.*, 2010, **10**, 1858. (e) D. Ganjewala, S. Kumar and R. Luthra, *Curr. Issues Mol. Biol.*, 2009, **11** (Suppl. 1), i35. (f) N. Singh, G. Cheve, M. A. Avery and C. R. McCurdy, *Curr. Pharm. Des.*, 2007, **13**, 1161. (g) P. J. Proteau, *Bioorg. Chem.*, 2004, **32**, 483.
- (a) S. Rosa-Putra, A. Disch, J. M. Bravo and M. Rohmer, *FEMS Microbiol. Lett.*, 1998, **164**, 169–175. (b) M. Rohmer, *Nat. Prod. Rep.*, 1999, **16**, 565–574. (c) M. Rohmer, C. Grosdemange-Billiard, M. Seemann and D. Tritsch, *Curr. Opin. Invest. Drugs*, 2004, **5**, 154. (d) M. Rohmer, *Pure Appl. Chem.*, 2007, **79**, 739.
- T. Kuzuyama, T. Shimizu, S. Takahashi and H. Seto, *Tetrahedron Lett.*, 1998, **39**, 7913.
- H. Jomaa, J. Wiesner, S. Sanderbrand, B. Altincicek, C. Weidemeyer, M. Hintz, I. Türbachova, M. Eberl, J. Zeidler, H. K. Lichtenthaler, D. Soldati and E. Beck, *Science*, 1999, **285**, 1573.
- B. Lell, R. Ruangweerayut, J. Wiesner, M. A. Missinou, A. Schindler, T. Baranek, M. Hintz, D. Hutchinson, H. Jomaa and P. G. Kreamsner, *Antimicrob. Agents Chemother.*, 2003, **47**, 735.
- J. Wiesner and H. Jomaa, *Curr. Drug Targ.*, 2007, **8**, 3.
- (a) S. Borrmann, A. A. Adegnik, P. B. Matsiegui, S. Issifou, A. Schindler, D. P. Mawili-Mboumba, T. Baranek, J. Wiesner, H. Jomaa and P. G. Kreamsner, *J. Infest. Dis.*, 2004, **189**, 901. (b) S. Borrmann, S. Issifou, G. Esser, A. A. Adegnik, M. Ramharter, P. B. Matsiegui, S. Oyakhirome, D. P. Mawili-Mboumba, M. A. Missinou, J. F. Kun, H. Jomaa and P. G. Kreamsner, *J. Infest. Dis.*, 2004, **190**, 1534.
- For recent papers on the synthesis of fosmidomycin analogues see: (a) C. T. Behrendt, A. Kunfermann, V. Illarionova, A. Matheussen, M. K. Pein, T. Graewert, J. Kaiser, A. Bacher, W. Eisenreich, B. Illarionov, M. Fischer, L. Maes, M. Groll and T. Kurz, *J. Med. Chem.*, 2011, **54**, 6796. (b) M. Andaloussi, M. Lindh, C. Björkelid, S. Suresh, A. Wieckowska, H. Iyer, A. Karlén and M. Larhed, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5403. (c) M. Andaloussi, L. M. Henriksson, A. Wieckowska, M. Lindh, C. Björkelid, A. M. Larsson, S. Suresh, H. Iyer, B. R. Srinivasa, T. Bergfors, T. Unge, S. L. Mowbray, M. Larhed, T. A. Jones and A. Karlén, *J. Med. Chem.*, 2011, **54**, 4964. (d) L. Deng, J. Diao, P. Chen, V. Pujari, Y. Yao, G. Cheng, D. C. Crick, B. V. V. Prasad and Y. Song, *J. Med. Chem.*, 2011, **54**, 4721. (e) S. Ponaire, C. Zinglé, D. Tritsch, C. Grosdemange-Billiard and M. Rohmer, *Eur. J. Med. Chem.*, 2012, **51**, 277. (f) T. Bodill, A. C. Conibear, M. K. M. Mutorwa, J. L. Goble, G. L. Blatch, K. A. Lobb, R. Klein and P. T. Kaye, *Bioorg. Med. Chem.*, 2013, **21**, 4332. (g) A. T. Nguyen-Trung, D. Tritsch, C. Grosdemange-Billiard and M. Rohmer, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1643. (h) G. San Jose, E. R. Jackson, R. Uh, C. Johny, A. Haymond, L. Lundberg, C. Pinkham, K. Kehn-Hall, H. I. Boshoff, R. D. Couch and C. S. Dowd, *Chem. Med. Comm.*, 2013, 1099. (i) A. M. Jansson, A. Więckowska, C. Björkelid, S. Yahiaoui, S. Sooriyaarachchi, M. Lindh, T. Bergfors, S. Dharavath, M. Desroses, S. Suresh, M. Andaloussi, R. Nikhil, S. Sreevalli, B. R. Srinivasa, M. Larhed, T. A. Jones, A. Karlén and S. L. Mowbray, *J. Med. Chem.*, 2013, **56**, 6190. (j) S. Montel, C. Midrier, J.-N. Volle, R. Braun, K. Haaf, L. Willms, J.-L. Pirat and D. Virieux, *Eur. J. Org. Chem.*, 2012, 3237–3248.
- M. Fellermeier, K. Kis, S. Sagner, U. Maier, A. Bacher and M. H. Zenk, *Tetrahedron Lett.*, 1999, **40**, 2743.
- Y. Kamuro, T. Kawai and T. Kakiushi, *Fujisawa Pharmaceutical Co. Ltd, Eur. Pat.* 0256785A2, 1988.
- A. Mac Sweeney, R. Lange, A. d'Arcy, A. Douangamath, J.-P. Surivet and C. Oefner, *J. Mol. Biol.*, 2005, **345**, 115.
- (a) J. W. Munos, X. Pu, S. O. Mansoorabadi, H. J. Kim and H.-W. Liu *J. Am. Chem. Soc.*, 2009, **131**, 2048. (b) U. Wong and R. J. Cox, *Angew. Chem. Int. Ed.*, 2007, **46**, 4926. (c) A. Mac Sweeney, R. Lange, R. P. M. Fernandes, H. Schulz, G. E. Dale, A. Douangamath, P. J. Proteau and C. Oefner, *J. Mol. Biol.*, 2005, **345**, 115. (d) A. Argyrou and J. S. Blanchard, *Biochemistry*, 2004, **43**, 4375. (e) K. Reuter, S. Sanderbrand, H. Jomaa, J. Wiesner, I. Steinbrecher, E. Beck, M. Hintz, G. Klebe and M. T. Stubbs, *J. Biol. Chem.*, 2002, **277**, 5378.
- (a) K. E. Pallett, J. P. Little, M. Sheekey and P. Veerasekaran, *Pestic. Biochem. Physiol.*, 1998, **62**, 113. (b) F. Viviani, J. P. Little and K. E. Pallett, *Pestic. Biochem. Physiol.*, 1998, **62**, 125.
- L. Deng, S. Sundriyal, V. Rubio, Z.-Z. Shi and Y. Song, *J. Med. Chem.*, 2009, **52**, 6539.
- (a) P. Nikitina, L. G. Kuz'mina, V. P. Perevalov and I. I. Tkach, *Tetrahedron*, 2013, **69**, 3249. (b) L. Wolff, *Justus Liebigs Ann. Chem.*, 1902, **325**, 129. (c) J. Lifschitz, *Chem. Ber.*, 1913, **46**, 3233.
- T. Majid, C. R. Hopkins, B. Pedgrift and N. Collar, *Tetrahedron Lett.*, 2004, **45**, 2137.
- R. Ortmann, J. Wiesner, K. Silber, G. Klebe, H. Jomaa and M. Schlitzer, *Arch. Pharm. Chem. Life Sci.*, 2007, **340**, 483.
- M. Witschel, *Bioorg. Med. Chem.*, 2009, **17**, 4221.
- S. S. Nikam, B. E. Komberg, D. R. Johnson and A. M. Doherty, *Tetrahedron Lett.*, 1995, **36**, 197.
- B. L. Eriksen, P. Vedso, S. Morel, M. Begtrup, *J. Org. Chem.*, 1998, **63**, 12.
- Crystal single structures were deposited at the Cambridge Crystallographic Data Centre and referenced with numbers: CCDC 959100 (**2a**); CCDC 959101 (**2b**) and CCDC 959102 (**2d**). All crystallographic data are free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- C. E. Griffin and S. K. Kundu, *J. Org. Chem.*, 1969, 1532.
- P. Mitula and C. Wawrzęńczyk, *ARKIVOC*, 2012, **4**, 216.
- G. Just, P. Potvin and G. H. Hakimelahi, *Can. J. Chem.*, 1980, **58**, 2780.