New Synthetic Approach for the Incorporation of 3-Hydroxypyridin-2(1*H*)-one (3,2-HOPO) Ligands: Synthesis of Structurally Diverse Poly 3,2-HOPO Chelators

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Abstract: The 3,2-HOPO sulfonamide reagent **3** was prepared from commercial 2,3-dihydroxypyridine in four steps in good yields. Sulfonamide **3** readily underwent selective alkylation with dibromides in the presence of base or could be coupled to alcohols using Mitsunobu conditions. The utility of this nucleophilic 3-hydroxypyridin-2(1*H*)-one (3,2-HOPO) reagent was demonstrated by the synthesis of some tris- and tetrakis-3,2-HOPO chelators. This approach for tethering 3,2-HOPO ligands is unique and flexible as shown by the preparation of 3,2-HOPO/iminocarboxylic acid chelator **17**.

Key words: 3-hydroxypyridin-2(1*H*)-one, synthesis, polydentate chelators, mixed ligand chelators, sulfonamide

There has been much recent interest in the synthesis of chelators containing the 3-hydroxypyridin-2(1*H*)-one (3,2-HOPO) ligand arising from their ability to form strong complexes with hard metal ions.[1] 3,2-HOPO chelators have been examined for a variety of medical applications including the treatment of iron overload diseases,[2] cancer treatment,[3] and as contrast agents in magnetic resonance imaging (MRI).[4] Hydroxypyridinone chelators also form strong complexes with actinide(IV) ions leading to possible applications in environmental remediation and biological detoxification.[5] Recently, the syntheses of HOPO chelators which also carry other ligand groups, such as hydroxamates, have been reported due to their potential biomedical applications.[6]

The direct alkylation of 2,3-dihydroxypyridine can be accomplished, but requires harsh conditions and, hence, is not a convenient method for the preparation of polydentate chelators.[7] The preferred approach that has been used to introduce the 3,2-HOPO ligand involved the reaction of an amine in the spacer moiety with an activated carboxylic acid linker attached to the pyridinone ring system followed by removal of protecting groups to expose the free ligand. 3,2-HOPO has been linked to the amine spacer either through an activated ester on the ring nitrogen as depicted in **I** (Figure 1), or through an activated carboxylic acid group on the pyridinone ring, see **II**. While the resulting amide linkages may be advantageous in the metal ion complexation process, they can lead to polydentate chelators with reduced organic and aqueous solubility that can limit their efficacy in the desired applications.

A while ago, we disclosed a method for introduction of 3,2-HOPO moieties onto a variety of nucleophilic platforms including polyamines[8] and polyphenols[9] that uses novel bicyclic 3,2-HOPO imidate electrophiles **III**. While **IIIa** and **IIIb** reacted readily with secondary amines, their reaction with aliphatic primary amines generally gave amidine products, limiting the use of this methodology for the introduction of 3,2-HOPO ligands onto amine platforms.

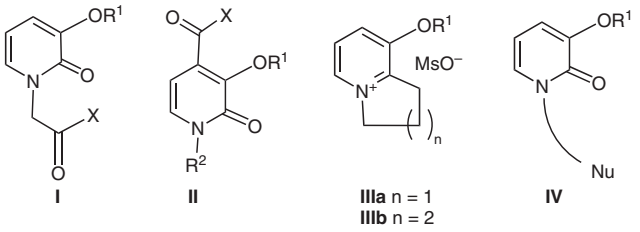

Figure 1

A synthon, such as **IV**, that allows the 3,2-HOPO ligand to serve as a nucleophile rather than as an electrophile would permit access to a diverse array of 3,2-HOPO ligands including mixed ligand systems and would complement existing methodology. In this paper, we report the preparation and applications of a nucleophilic 3,2-HOPO sulfonamide reagent **3** that can be effectively tethered onto suitable platforms by alkylation reactions. This reagent allows access to new classes of 3,2-HOPO chelators including mixed ligand systems.

The first challenge was to establish a convenient method for the preparation of 3,2-HOPO amine **2** (Scheme 1). In contrast to alkylation reactions, which require harsh conditions, 2,3-dihydroxypyridine undergoes Michael additions more readily. Reaction of 2,3-dihydroxypyridine with acrylonitrile in the presence of cesium fluoride catalyst in acetonitrile at 60 °C gave the corresponding nitrile adduct in good yield and sufficient purity for direct use in the next step. Treatment of the crude nitrile with benzyl bromide and potassium carbonate in refluxing acetonitrile gave benzyl-protected 3,2-HOPO nitrile **1**, which was conveniently purified by washing with diethyl ether. Selective reduction of the nitrile in the presence of the pyri-

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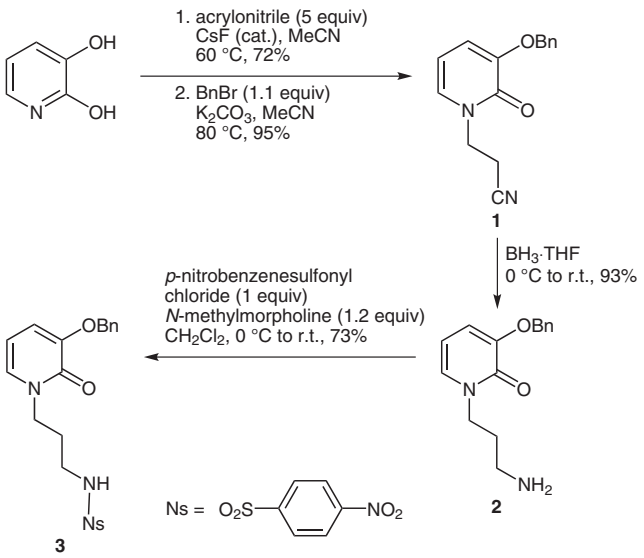
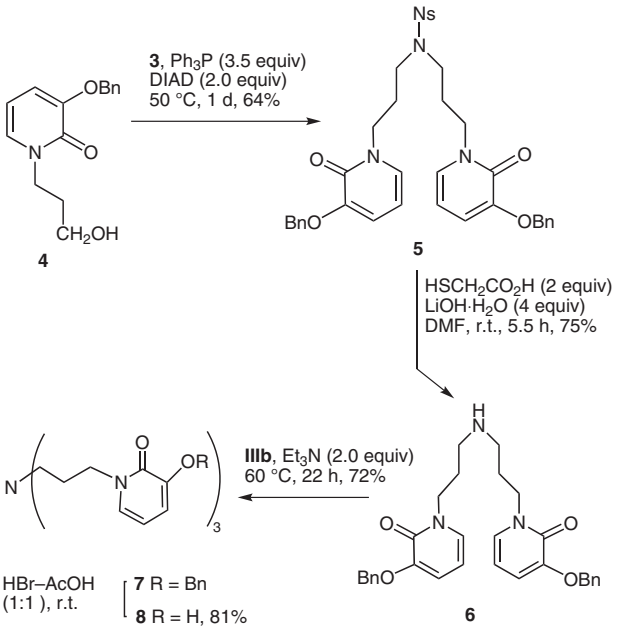
dinone ring was a major concern.[10] However, selective reduction of the nitrile to the corresponding 3,2-HOPO amine **2** could be achieved using borane–tetrahydrofuran complex. It was found that the best method for the isolation of the free 3,2-HOPO amine **2** involved quenching the reaction mixture with methanol followed by stirring with concentrated hydrochloric acid for 24 hours. After adjusting the pH of the mixture to 8 with sodium hydroxide, the 3,2-HOPO amine **2** could be extracted into dichloromethane and isolated in 93% yield with satisfactory purity.[11] The desired 3,2-HOPO amine could be readily prepared on a large scale without the need for chromatographic purification.

The amine **2** is a useful 3,2-HOPO synthon, as it can be coupled using standard procedures to various activated acid derivatives like **I** and **II**. However, we were interested in its alkylation reactions that could lead to new chelators without the geometric constraints imposed by amide linkages. In order to achieve selective monoalkylations, it was thought best to use the corresponding 4-nitrobenzenesulfonyl (nosyl) derivative of **2**. Treatment of 3,2-HOPO amine **2** with 4-nitrobenzenesulfonyl chloride in the presence of *N*-methylmorpholine (1.2 equiv) in dichloromethane gave the desired 3,2-HOPO sulfonamide reagent **3** as a light-yellow solid in 73% yield after chromatographic purification.



Scheme 1 Synthesis of 3,2-HOPO sulfonamide **3**

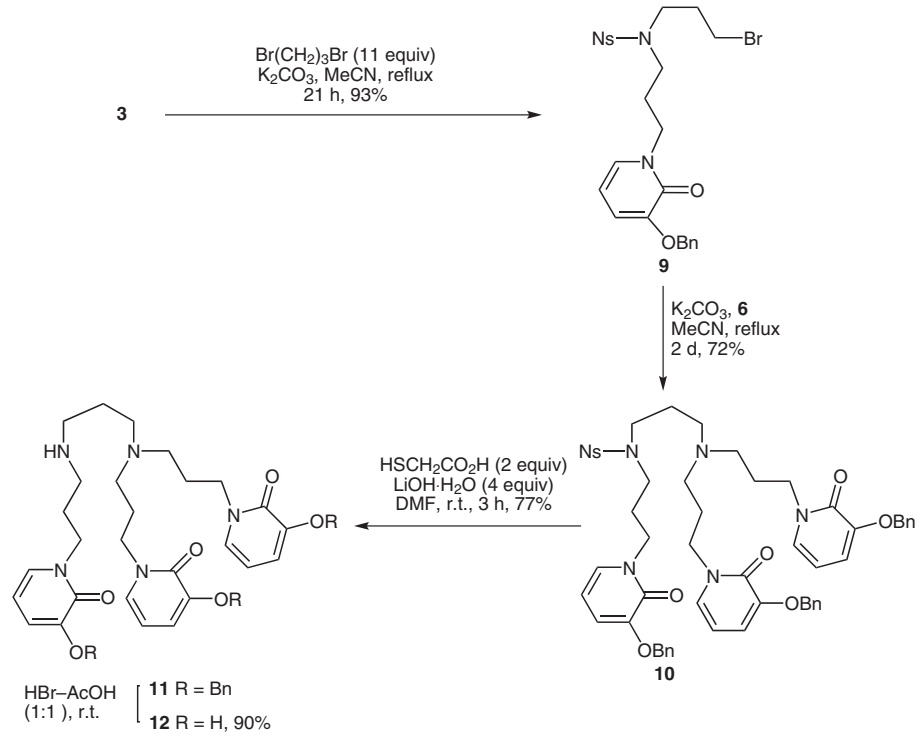
With the nosyl reagent **3** in hand, it was decided that the best way to demonstrate its synthetic utility was by the synthesis of polydentate chelators such as the tripodal TREN-based tris-3,2-HOPO chelator **8** shown in Scheme 2. TREN-based 3,2-HOPO and hydroxamate chelators have been of much interest for the binding of hard metal ions.[12] Reaction of the sulfonamide reagent **3** using triphenylphosphine and diisopropyl azodicarboxylate in tetrahydrofuran at 50 °C with 3,2-HOPO alcohol **4**[8a] gave the nosyl-bis-3,2-HOPO amine **5** in 64% yield after silica gel chromatography. Attempts to remove the nosyl group using DBU and thioglycerol in *N*,*N*-dimethylformamide gave complex mixtures that were difficult to purify. However, the nosyl group could be easily cleaved with thioacetic acid and lithium hydroxide in *N*,*N*-dimethylformamide at room temperature to furnish the bis-3,2-HOPO amine **6** in 75% yield after purification.[13,14] Alkylation of the secondary amine **6** with 3,2-HOPO imidate salt **IIIb** in the presence of excess of triethylamine in acetonitrile at 60 °C gave **7** in good yield after purification.[8a] Removal of the benzyl groups using hydrobromic acid–acetic acid (1:1) gave the target tris-3,2-HOPO chelator **8** as its hydrobromide salt in 81% yield.



Scheme 2 Synthesis of tris-3,2-HOPO chelator **8**

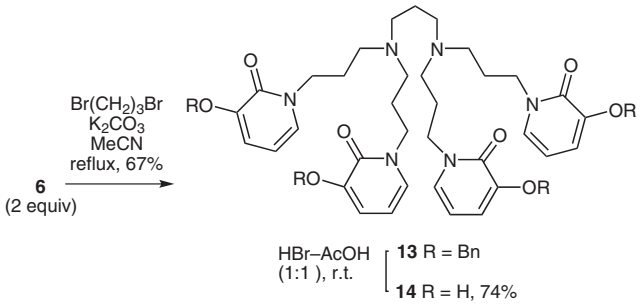
The availability of structurally diverse diamines has made them a well-exploited spacer group for the introduction of ligand moieties. Hence, the tris-3,2-HOPO **12** and tetrakis-3,2-HOPO **14** assembled on a propane-1,3-diamine platform were attractive targets to demonstrate the usefulness of our methodology. To our satisfaction, the monoalkylation of **3** could be achieved in high yields using excess 1,3-dibromopropane in the presence of potassium carbonate in refluxing acetonitrile to give **9** in excellent yield (Scheme 3). Further alkylation of **9** with bis-3,2-HOPO amine **6** followed by removal of the nosyl group gave **11**. Debenzylation using standard reaction conditions gave the tris-3,2-HOPO chelator **12** as the hydrobromide salt. It is important to point out that the diamine platform of **12** can be easily modified by the use of other dibromides in the initial alkylation of **3**.

The above synthetic scheme was readily modified to prepare tetrakis-3,2-HOPO chelators, a class of compounds which have been of interest for their actinide ion binding (Scheme 4).[5] The alkylation of 1,3-dibromopropane (1 equiv) with two equivalents of bis-3,2-HOPO amine **6** using potassium carbonate in refluxing acetonitrile gave the



Scheme 3 Synthesis of tris-3,2-HOPO chelator **12**

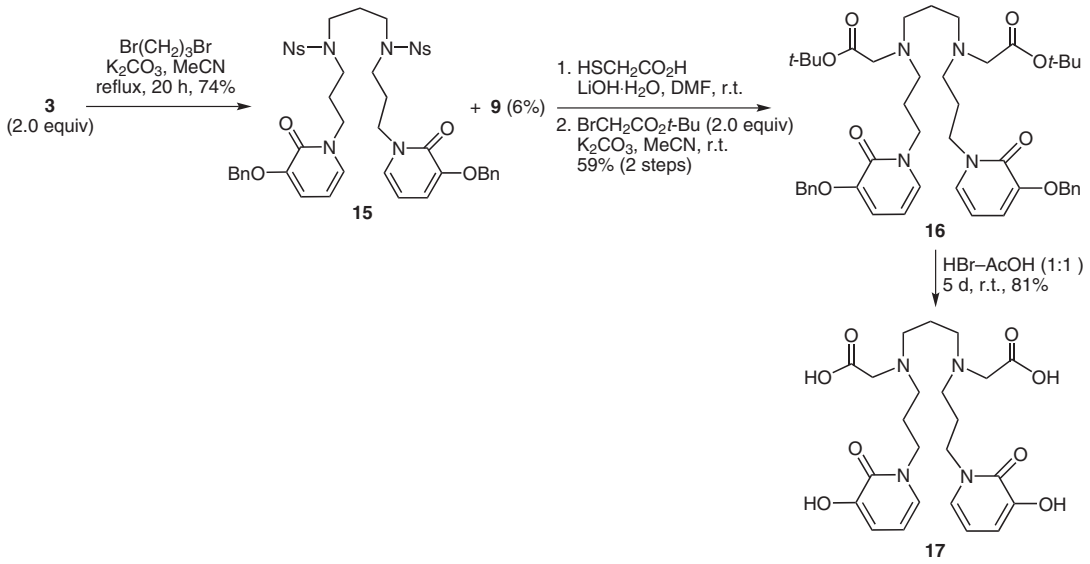
corresponding tetrabenzyl-protected 3,2-HOPO **13** in good yield after purification. Removal of the benzyl protecting groups gave the tetrakis-3,2-HOPO chelator **14** as the hydrobromide salt.



Scheme 4 Synthesis of tetrakis-3,2-HOPO chelator **14**

Finally, it was felt relevant to demonstrate the use of this methodology to make a mixed 3,2-HOPO ligand system. The ability to access mixed 3,2-HOPO ligand chelators, carrying other metal-binding ligands such as iminocarboxylic acids and hydroxamic acids would provide new classes of molecules with interesting coordination chemistry and biological activity.[6] The iminoacetic acid/3,2-HOPO chelator **17** was chosen as a target for this synthetic study. Dialkylation of 1,3-dibromopropane with two equivalents of sulfonamide 3,2-HOPO **3** gave the desired bis-3,2-HOPO **15** in 74% yield along with 6% of the monoalkylated product **9**. The nosyl groups of **15** were removed using standard conditions and the resulting diamine was used without purification. Dialkylation of the crude diamine with *tert*-butyl bromoacetate in acetonitrile in the presence of potassium carbonate gave **16** in 59% yield for two steps after purification. The concurrent removal of both benzyl and *tert*-butyl protecting groups in the last step using hydrobromic acid/acetic acid (1:1) is a matter of convenience and gave the desired mixed ligand chelator **17** as a light-brown solid (Scheme 5). The chelator **17** is water soluble as might be expected.

In conclusion, the development of strategies and synthetic methodologies for the incorporation of the 3,2-HOPO moiety into a diverse array of platforms is of great importance due to the potential environmental and biomedical applications of these metal ion chelators. The chemistry presented in this paper is applicable to the synthesis of a broad array of polydentate 3,2-HOPO targets and related analogues. The amine **2** can be prepared from commercially available material in three steps and is a useful reagent for direct coupling with carboxylic acids to tether the 3,2-HOPO moiety. It can be converted into its nosyl derivative **3** in good yields. The sulfonamide **3** can undergo selective alkylation reactions with dibromides or can participate in Mitsunobu reactions with alcohols under mild conditions. The usefulness of this synthetic approach has been demonstrated by the synthesis of some novel tris- and tetrakis-3,2-HOPO chelators. The synthesis of mixed 3,2-HOPO-iminoacetic acid chelator **17**, highlights the use of this method to access desired mixed ligand targets. Also, the approach is amenable to the preparation of hexadentate chelators such as tris-3,2-HOPO **11** which have a functional handle for the introduction of a fluorescent reporter group[15] or attachment to other biomolecules[16] of interest.



Scheme 5 Synthesis of mixed 3,2-HOPO/iminoacetic acid chelator **17**

^{1}H (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Varian XL 200. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a 300 MHz Varian NMR. ^{1}H NMR (400 MHz) spectra were recorded on a Varian Unity 400 spectrometer. NMR spectral samples were prepared in $CDCl_3$ relative to TMS or D_2O as noted. For ^{1}H NMR spectra obtained in D_2O, the HOD peak at δ = 4.72 ppm was used as internal reference. For ^{13}C NMR spectra obtained in D_2O, 1,4-dioxane (δ = 66.5) was used as an internal reference. Analytical and preparative TLC was performed on silica 60/F254 plastic plates (EM Science). Column chromatography was performed on silica gel (Merck 60–200 mesh) or basic alumina (Aldrich 150 mesh). Chromatography solvents were reagent grade and were obtained from either Fisher Scientific or VWR Scientific. Reagents were obtained from Aldrich or Lancaster chemical companies and were used as received. Anhyd THF was collected from a GlassContour™ solvent purification system. Other dry solvents (MeCN, CH_2Cl_2, etc) were obtained from Acros. Desert Analytics (Tucson, Arizona) performed elemental analyses.

3-(3-Hydroxy-2-oxopyridin-1(2*H*)-yl)propanenitrile and 3-[3-(Benzyloxy)-2-oxopyridin-1(2*H*)-yl]propanenitrile (1)

3-(3-Hydroxy-2-oxopyridin-1(2*H*)-yl)propanenitrile

To a soln of 2,3-dihydroxypyridine (10.0 g, 90 mmol) in MeCN (110 mL) was added CsF (1.37 g, 9 mmol) and acrylonitrile (29 mL, 450 mmol) and the soln was heated at reflux for 3 d. The solvent and excess acrylonitrile were removed in vacuo. The product was dissolved in hot MeCN (2 × 100 mL) and the solids were filtered off. The solvent was removed under reduced pressure and the resulting solid washed with cold H_2O (50 mL) at 0 °C for 1 h. The product was collected by vacuum filtration and then dried under reduced pressure to give the crude nitrile as a solid (10.7 g, 72%), which was used without purification.

IR (neat): 3217, 2247, 1656, 1605 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.93 (t, *J* = 6.2 Hz, 2 H), 4.23 (t, *J* = 6.2 Hz, 2 H), 6.24 (t, *J* = 7.3 Hz, 1 H), 6.76–6.94 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.3, 46.4, 107.5, 114.7, 116.8, 126.9, 146.7, 158.4.

3-[3-(Benzyloxy)-2-oxopyridin-1(2*H*)-yl]propanenitrile (1)

To a soln of the crude nitrile (7.0 g, 42.6 mmol) in MeCN (70 mL) was added K_2CO_3 (6.48 g, 46.9 mmol) and BnBr (5.6 mL, 46.9 mmol) and the mixture was heated at reflux for 19 h. The solvent and excess BnBr were removed in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with sat. $NaHCO_3$ (2 × 60 mL). The aqueous layer was extracted once more with CH_2Cl_2 (40 mL). The combined organic layers were then washed with sat. NaCl (2 × 100 mL), dried ($MgSO_4$), and filtered. The solid product was washed with Et_2O (2 × 50 mL) and collected via vacuum filtration. The white crystalline product was dried under reduced pressure to give nitrile **1** (10.3 g, 95%); mp 138–140 °C.

IR (KBr): 2946, 2246, 1652, 1611, 1457 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.94 (t, *J* = 6.6 Hz, 2 H), 4.19 (t, *J* = 6.6 Hz, 2 H), 5.12 (s, 2 H), 6.11 (t, *J* = 7.0 Hz, 1 H), 6.70 (dd, *J* = 1.5, 7.7 Hz, 1 H), 6.98 (dd, *J* = 1.5, 7.0 Hz, 1 H), 7.30–7.46 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.9, 46.2, 70.7, 105.2, 115.9, 117.1, 127.2, 128.0, 128.4, 128.8, 135.9, 148.8, 157.7.

Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.46; H, 5.25; N, 10.89.

3-[3-(Benzyloxy)-2-oxopyridin-1(2*H*)-yl]propanamine (2)

To a soln of nitrile **1** (2.00 g, 7.87 mmol) in anhyd THF (40 mL) at 0 °C was added BH_3·THF (11.6 mL, 11.7 mmol) and the soln stirred at r.t. for 39 h. The mixture was cooled to 0 °C, quenched with MeOH and the solvent removed in vacuo. The crude product was dissolved in MeOH (40 mL), cooled to 0 °C, and the pH adjusted to 2 with concd HCl. After stirring at r.t. for 24 h, the solvent was removed in vacuo and the resulting thick oil was washed with EtOAc (3 × 5 mL). The remaining residue was dissolved in H_2O (15 mL) and cooled to 0 °C. The pH was adjusted to 8 with 20% aq NaOH and the product extracted into CH_2Cl_2 (3 × 100 mL), dried (Na_2SO_4), and filtered and the solvent was removed in vacuo. The crude amine **2** (1.88 g, 93%) was dried under reduced pressure and used without purification.[11]

IR (neat): 3367, 2944, 1652, 1601 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86–1.93 (m, 2 H), 2.71 (t, *J* = 6.6 Hz, 2 H), 4.09 (t, *J* = 6.8 Hz, 2 H), 5.12 (s, 2 H), 6.03 (t, *J* = 7.0 Hz, 1 H), 6.64 (dd, *J* = 1.7, 7.2 Hz, 1 H), 6.92 (dd, *J* = 1.8, 6.8 Hz, 1 H), 7.30–7.45 (m, 5 H).

***N*-{3-[3-(Benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}-4-nitrobenzenesulfonamide (3)**

A soln of 4-nitrobenzenesulfonyl chloride (0.96 g, 4.33 mmol) in CH_2Cl_2 (10 mL) was added to a soln of amine **2** (1.12 g, 4.34 mmol) and *N*-methylmorpholine (0.57 mL, 5.19 mmol) in CH_2Cl_2 at 0 °C. After stirring at r.t. for 4 h, the solvent was removed in vacuo and the residue dissolved in 15% CH_2Cl_2–EtOAc (80 mL). The organic layer was washed with H_2O (2 × 50 mL) and dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by chromatography (silica gel, 30% EtOAc–hexane to 2% MeOH–$CHCl_3$) to give sulfonamide 3,2-HOPO **3** (1.41 g, 73%) as a pale-yellow solid; mp 165–167 °C.

IR (KBr): 3103, 1652, 1599, 1521 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.92–1.98 (m, 2 H), 2.85–2.89 (m, 2 H), 4.12 (t, *J* = 6.3 Hz, 2 H), 5.09 (s, 2 H), 6.12 (t, *J* = 7.0 Hz, 1 H), 6.67 (dd, *J* = 1.4, 7.4 Hz, 1 H), 6.84 (dd, *J* = 1.6, 6.8 Hz, 1 H), 6.92 (unres t, 1 H), 7.33–7.43 (m, 5 H), 8.08 (d, *J* = 8.8 Hz, 2 H), 8.26 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$ with a few drops of CD_3OD): δ = 29.6, 39.4, 46.2, 70.8, 106.3, 115.9, 124.1, 127.3, 128.2, 128.4, 128.6, 135.7, 146.2, 148.6, 149.8, 158.6.

Anal. Calcd for $C_{21}H_{21}N_3O_6S$: C, 56.87; H, 4.77; N, 9.48. Found: C, 56.57; H, 4.94; N, 9.18.

***N*,*N*-Bis{3-[3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}-4-nitrobenzenesulfonamide (5)**

A soln of 3,2-HOPO alcohol **4** (0.591 g, 2.28 mmol) in anhyd THF (10 mL) was added to a suspension of sulfonamide 3,2-HOPO **3** (1.01 g, 2.28 mmol) and Ph_3P (2.09 g, 7.97 mmol) in THF (15 mL) and the mixture stirred at r.t. for 5 min. DIAD (0.88 mL, 4.54 mmol) was slowly added and the mixture heated at 50 °C for 24 h. The solvent was removed under reduced pressure and the residue purified by chromatography (silica gel, 60–90% EtOAc–hexane) to give sulfonamide **5** (0.99 g, 64%) as a light-red solid; mp 45–46 °C.

IR (KBr): 1654, 1603, 1528 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.02–2.12 (m, 4 H), 3.25 (t, *J* = 7.6 Hz, 4 H), 4.01 (t, *J* = 7.3 Hz, 4 H), 5.10 (s, 4 H), 6.04 (t, *J* = 7.3 Hz, 2 H), 6.65 (dd, *J* = 1.8, 7.3 Hz, 2 H), 6.95 (dd, *J* = 1.7, 7.0 Hz, 2 H), 7.32–7.44 (m, 10 H), 7.92 (d, *J* = 9.1 Hz, 2 H), 8.33 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.4, 46.4, 47.3, 70.8, 105.0, 115.5, 124.5, 127.3, 128.0, 128.3, 128.5, 128.9, 136.2, 144.6, 148.8, 150.0, 158.1.

Anal. Calcd for $C_{36}H_{36}N_4O_8S·0.5H_2O$: C, 62.32; H, 5.38; N, 8.08. Found: C, 62.03; H, 5.18; N, 8.19.

***N*,*N*-Bis{3-[3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}amine (6)**

Mercaptoacetic acid (0.24 mL, 3.45 mmol) and $LiOH·H_2O$ (0.303 g, 7.22 mmol) were added to a soln of sulfonamide 3,2-HOPO **5** (1.17 g, 1.71 mmol) in DMF (5 mL) and the mixture stirred at r.t. for 5.5 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (80 mL) and washed with sat. $NaHCO_3$ (3 × 60 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure. The crude product was purified by column chromatography (basic alumina, 0–10% MeOH–EtOAc) to give amine **6** (0.64 g, 75%) as a viscous red oil.

IR (neat): 3302, 1652, 1602 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.90–1.97 (m, 4 H), 2.59 (t, *J* = 6.6 Hz, 4 H), 4.08 (t, *J* = 6.8 Hz, 4 H), 5.11 (s, 4 H), 6.00 (t, *J* = 7.2 Hz, 2 H), 6.62 (dd, *J* = 1.8, 7.4 Hz, 2 H), 6.96 (dd, *J* = 1.6, 6.8 Hz, 2 H), 7.29–7.44 (m, 10 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.4, 46.0, 47.3, 70.8, 104.5, 115.7, 127.3, 127.9, 128.5, 129.3, 136.4, 148.8, 158.2.

Anal. Calcd for $C_{30}H_{33}N_3O_4·0.12CHCl_3$: C, 70.39; H, 6.50; N, 8.18. Found: C, 70.08; H, 6.44; N, 8.37.

Tris{3-[3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}amine (7)

A soln of Et_3N (0.17 mL, 1.22 mmol) in anhyd MeCN (1 mL) was added to a soln of benzyl-protected 3,2-HOPO amine **6** (0.30 g, 0.6 mmol) in anhyd MeCN (2 mL). A soln of 3,2-HOPO iminium salt **IIIb**[11] (0.30 g, 0.90 mmol) in MeCN (6 mL) was added and the mixture was heated at 60 °C for 22 h. The volatiles were removed under reduced pressure and the residue purified on basic alumina (0–2% MeOH–EtOAc). The benzyl-protected tris-3,2-HOPO **7** (0.32 g, 72%) was obtained as a viscous brown oil.

IR (neat): 1651, 1603, 1555 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.87–1.95 (m, 6 H), 2.52 (t, *J* = 6.6 Hz, 6 H), 4.06 (t, *J* = 7.6 Hz, 6 H), 5.09 (s, 6 H), 6.00 (t, *J* = 7.0 Hz, 3 H), 6.62 (dd, *J* = 1.4, 7.4 Hz, 3 H), 6.99 (dd, *J* = 1.2, 7.0 Hz, 3 H), 7.27–7.44 (m, 15 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.4, 48.4, 50.4, 70.6, 104.5, 115.3, 127.2, 127.9, 128.5, 129.4, 136.3, 148.7, 158.0.

Anal. Calcd for $C_{45}H_{48}N_4O_6$: C, 72.95; H, 6.53; N, 7.56. Found: C, 73.17; H, 6.66; N, 7.42.

Tris{3-[3-hydroxy-2-oxopyridin-1(2*H*)-yl]propyl}amine Tetrahydrobromide (8·4HBr)

Benzyl-protected tris-3,2-HOPO amine **7** (0.30 g, 0.412 mmol) was dissolved in concd HBr–AcOH (1:1, 20 mL) and stirred at r.t. for 67 h. The volatiles were removed under reduced pressure. The residue was washed with EtOAc and Et_2O and dried under high vacuum for 24 h. The product was lyophilized to yield tris-3,2-HOPO chelator **8** (0.264 g, 81%) as a light brown tetrahydrobromide salt.

IR (KBr): 3408, 1645, 1543 cm^{-1}.

^1H NMR (D_2O, 300 MHz): δ = 1.96–2.06 (m, 6 H), 3.09–3.14 (m, 6 H), 3.98 (t, *J* = 7.0 Hz, 6 H), 6.30 (t, *J* = 7.0 Hz, 3 H), 6.89 (dd, *J* = 1.8, 7.6 Hz, 3 H), 7.07 (dd, *J* = 1.8, 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, D_2O): δ = 23.2, 46.7, 49.7, 109.0, 118.8, 128.8, 145.4, 158.3.

Anal. Calcd for $C_{24}H_{30}N_4O_6·4HBr$: C, 36.30; H, 4.32; N, 7.05. Found: C, 36.05; H, 4.22; N, 6.89.

***N*-{3-[3-(Benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}-*N*-(3-bromopropyl)-4-nitrobenzenesulfonamide (9)**

Sulfonamide 3,2-HOPO **3** (0.60 g, 1.35 mmol) and 1,3-dibromopropane (1.5 mL, 14.8 mmol) were dissolved in anhyd MeCN (12 mL) followed by the addition of K_2CO_3 (0.37 g, 2.70 mmol) and the mixture was heated at reflux for 21 h. The solvent was removed under reduced pressure. The residue was diluted with EtOAc (60 mL), washed with H_2O (2 × 20 mL), and dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by chromatography (silica gel, 50–60% EtOAc–hexane) to give **9** (0.712 g, 93%) as a viscous yellow oil.

IR (neat): 1652, 1603, 1531 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.08–2.16 (m, 4 H), 3.25–3.33 (m, 4 H), 3.40 (t, *J* = 6.5 Hz, 2 H), 4.02 (t, *J* = 7.0 Hz, 2 H), 5.11 (s, 2 H), 6.08 (t, *J* = 6.8 Hz, 1 H), 6.67 (d, *J* = 7.0 Hz, 1 H), 6.94 (d, *J* = 6.6 Hz, 1 H), 7.31–7.44 (m, 5 H), 7.98 (d, *J* = 8.0 Hz, 2 H), 8.37 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.5, 31.9, 33.9, 48.9, 49.4, 49.5, 72.8, 107.1, 117.5, 126.5, 129.4, 130.1, 130.4, 130.6, 130.8, 138.2, 146.8, 151.0, 152.2, 160.2.

Anal. Calcd for $C_{24}H_{26}BrN_3O_6S·0.8CHCl_3$: C, 45.13; H, 4.09; N, 6.37. Found: C, 45.40; H, 4.44; N, 6.67.

N-{3-[3-(Benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}-*N*-[3-(bis{3-[3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}amino)propyl]-4-nitrobenzenesulfonamide (10)

A soln of bromide **9** (0.64 g, 1.14 mmol) in anhyd MeCN (15 mL) was added to a suspension of benzyl-protected 3,2-HOPO amine **6** (0.53 g, 1.06 mmol) and K_2CO_3 (0.59 g, 4.2 mmol) in anhyd MeCN (15 mL) and the mixture heated at reflux for 48 h. The solvent was removed under reduced pressure and the residue was diluted with $CHCl_3$ (60 mL) and washed with sat. $NaHCO_3$ (1 × 40 mL). The aqueous layer was again extracted with $CHCl_3$ (1 × 40 mL) and the combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified on basic alumina (60–70% EtOAc–hexane to 2% MeOH–EtOAc) to give **10** (0.749 g, 72%) as a yellow solid; mp 42–43 °C.

IR (neat): 1652, 1603, 1528 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.71–1.80 (m, 2 H), 1.83–1.92 (m, 4 H), 2.00–2.10 (m, 2 H), 2.40–2.49 (m, 6 H), 3.22 (t, *J* = 7.3 Hz, 2 H), 3.33 (t, *J* = 9.1 Hz, 2 H), 3.97–4.03 (m, 6 H), 5.08 (s, 2 H), 5.09 (s, 4 H), 5.97–6.03 (m, 3 H), 6.63 (dd, *J* = 1.5, 7.6 Hz, 3 H), 6.97 (d, *J* = 6.7 Hz, 3 H), 7.26–7.43 (m, 15 H), 8.01 (d, *J* = 8.8 Hz, 2 H), 8.32 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.4, 26.9, 28.4, 46.4, 47.3, 47.6, 48.3, 50.6, 50.8, 70.6, 104.4, 104.7, 115.2, 115.4, 124.4, 127.2, 127.8, 128.3, 129.1, 129.2, 136.1, 136.2, 144.8, 148.7, 149.8, 157.8, 157.9.

Anal. Calcd for $C_{54}H_{58}N_6O_{10}S·0.4CHCl_3$: C, 63.38; H, 5.71; N, 8.15. Found: C, 63.47; H, 5.64; N, 8.41.

N,*N*,*N*′-Tris{3-[3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}propane-1,3-diamine (11)

Mercaptoacetic acid (0.132 mL, 1.9 mmol) and $LiOH·H_2O$ (0.16 g, 3.8 mmol) were added to a soln of sulfonamide **10** (0.94 g, 0.95 mmol) in DMF (6 mL) and the soln stirred at r.t. for 3 h. The solvent was removed under reduced pressure. The residue was diluted with $CHCl_3$ (80 mL) and washed with sat. $NaHCO_3$ (40 mL). The aqueous layer was again extracted with $CHCl_3$ (50 mL). The combined organic layers were washed with sat. $NaHCO_3$ (60 mL) and dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified on basic alumina (2–10% MeOH–EtOAc) to give amine **11** (0.590 g, 78%) as a red oil.

IR (neat): 3302, 1652, 1602 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.65 (m, 2 H), 1.85–1.97 (m, 6 H), 2.47 (t, *J* = 6.7 Hz, 6 H), 2.58–2.64 (m, 4 H), 3.97–4.06 (m, 6 H), 5.09 (s, 6 H), 5.95–6.02 (m, 3 H), 6.62 (dd, *J* = 1.5, 7.3 Hz, 3 H), 6.92–6.96 (m, 3 H), 7.28–7.44 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.4, 27.0, 29.3, 46.3, 47.3, 48.0, 48.3, 50.7, 51.5, 70.6, 104.4, 115.4, 127.2, 127.8, 128.4, 129.3, 136.3, 148.8, 158.0.

Anal. Calcd for $C_{48}H_{55}N_5O_6·0.7CHCl_3$: C, 66.35; H, 6.37; N, 7.94. Found: C, 66.73; H, 6.45; N, 8.31.

N,*N*,*N*′-Tris{3-[3-(hydroxy)-2-oxopyridin-1(2*H*)-yl]propyl}propane-1,3-diamine Tetrahydrobromide (12·4HBr)

Benzyl-protected 3,2-HOPO **11** (0.60 g, 0.745 mmol) was dissolved in concd HBr–AcOH (1:1, 28 mL) and the soln stirred at r.t. for 66 h. The volatiles were removed under reduced pressure. The residue was washed with EtOAc and Et_2O and dried under high vacuum for 24 h. The product was lyophilized to yield tris-3,2-HOPO chelator **12** (0.63 g, 90%) as the tetrahydrobromide salt.

IR (KBr): 3400, 2960, 1640, 1547 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 2.03–2.16 (m, 8 H), 3.01 (t, *J* = 7.4 Hz, 2 H), 3.08 (t, *J* = 7.6 Hz, 2 H), 3.17–3.27 (m, 6 H), 4.04–4.11 (m, 6 H), 6.35–6.40 (m, 3 H), 6.95–6.99 (m, 3 H), 7.12–7.16 (m, 3 H).

^{13}C NMR (50 MHz, D_2O): δ = 20.5, 23.2, 25.5, 44.2, 44.6, 46.6, 46.7, 49.9, 109.0, 118.9, 119.0, 129.0, 145.2, 145.3, 158.4, 158.6.

Anal. Calcd for $C_{27}H_{37}N_5O_6·4HBr·H_2O$: C, 37.31; H, 4.99; N, 8.06. Found: C, 37.53; H, 4.69; N, 8.38.

N,*N*,*N*′,*N*′-Tetrakis{3-[3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}propane-1,3-diamine (13)

1,3-Dibromopropane (30.6 μL, 0.30 mmol) was added to a suspension of benzyl-protected bis-3,2-HOPO **6** (0.30 g, 0.60 mmol) and K_2CO_3 (0.21 g, 1.5 mmol) in anhyd MeCN (6 mL) and the mixture was heated at reflux for 2 d. The solvent was removed under reduced pressure. The residue was diluted with $CHCl_3$ (50 mL) and washed with $NaHCO_3$ (30 mL). The aqueous layer was again extracted with $CHCl_3$ (30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified on basic alumina (2% MeOH–EtOAc) to provide benzyl-protected 3,2-HOPO **13** (0.21 g, 67%) as a viscous oil.

IR (neat): 2949, 2811, 1651, 1602, 1555 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.46–1.60 (m, 2 H), 1.84–1.93 (m, 8 H), 2.42–2.49 (m, 12 H), 3.99 (t, *J* = 7.6 Hz, 8 H), 5.07 (s, 8 H), 5.97 (t, *J* = 7.0 Hz, 4 H), 6.60 (dd, *J* = 1.7, 7.3 Hz, 4 H), 6.98 (dd, *J* = 1.7, 6.7 Hz, 4 H), 7.27–7.43 (m, 20 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7, 26.3, 48.2, 50.6, 51.5, 70.5, 104.4, 115.3, 127.2, 127.8, 128.4, 129.4, 136.2, 148.6, 157.9.

Anal. Calcd for $C_{63}H_{70}N_6O_8·0.5CHCl_3$: C, 69.40; H, 6.47; N, 7.65. Found: C, 69.33; H, 6.54; N, 7.68.

N,*N*,*N*′,*N*′-Tetrakis{3-[3-hydroxy-2-oxopyridin-1(2*H*)-yl]propyl}propane-1,3-diamine Hydrobromide Salt (14·HBr)

Benzyl-protected 3,2-HOPO **13** (0.13 g, 0.13 mmol) was dissolved in concd HBr–glacial AcOH (1:1, 10 mL) and stirred at r.t. for 4 d. The volatiles were removed under reduced pressure. The residue was washed with EtOAc and Et_2O and dried under high vacuum for 24 h. The product was lyophilized from H_2O–MeCN to yield tetrakis-3,2-HOPO chelator **14** (0.11 g, 74%) as a reddish hydrobromide salt.

IR (KBr): 2963, 1640, 1600, 1544 cm^{-1}.

^1H NMR (D_2O, 300 MHz): δ = 2.07–2.16 (m, 10 H), 3.17–3.26 (m, 12 H), 4.04 (t, *J* = 6.7 Hz, 8 H), 6.35 (t, *J* = 7.3 Hz, 4 H), 6.96 (dd, *J* = 1.7, 7.6 Hz, 4 H), 7.15 (dd, *J* = 1.7, 6.7 Hz, 4 H).

^{13}C NMR (50 MHz, D_2O): δ = 18.6, 23.3, 46.7, 49.8, 50.0, 109.0, 118.8, 128.9, 145.4, 158.4.

Anal. Calcd for $C_{35}H_{46}N_6O_8·5.7HBr$: C, 36.88; H, 4.57; N, 7.37; Found: C, 36.54; H, 4.77; N, 7.76.

N,*N*′-Bis{3-[3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}-*N*,*N*′-propane-1,3-diyldi-4-nitrobenzenesulfonamide (15)

K_2CO_3 (0.60 g, 4.4 mmol) was added to a soln of sulfonamide 3,2-HOPO **3** (0.78 g, 1.75 mmol) and 1,3-dibromopropane (0.18 g, 0.87 mmol) in anhyd MeCN (20 mL) and the mixture was heated at reflux for 20 h. The solvent was removed under reduced pressure and the residue was diluted with CH_2Cl_2 (40 mL), washed with H_2O (3 × 20 mL), and dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by chromatography (silica gel, 50–80% EtOAc–hexane) to give dialkylated compound **15** as a yellow solid (0.60 g, 74%) and monoalkylated compound **9** (0.064 g, 6%); mp 76–78 °C.

IR (KBr): 1654, 1604, 1528 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01–2.07 (m, 6 H), 3.22–3.26 (m, 8 H), 3.98 (t, *J* = 7.2 Hz, 4 H), 5.07 (s, 4 H), 6.04 (t, *J* = 7.2 Hz, 2 H), 6.66 (dd, *J* = 1.6, 7.6 Hz, 2 H), 6.94 (dd, *J* = 1.6, 6.8 Hz, 2 H), 7.30–7.41 (m, 10 H), 7.97 (d, *J* = 9.0 Hz, 4 H), 8.36 (d, *J* = 9.0 Hz, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.2, 28.7, 46.8, 47.6, 70.8, 105.0, 115.3, 124.5, 127.4, 128.1, 128.5, 129.0, 136.0, 144.5, 148.9, 150.1, 158.0.

Anal. Calcd for $C_{45}H_{46}N_6O_{12}S_2$: C, 58.30; H, 5.00; N, 9.07. Found: C, 58.46; H, 5.03; N, 9.28.

N,N′-Bis{3-[3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}propane-1,3-diamine and Di-*tert*-butyl N,N′-Bis{3-[3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}-2,2′-(propane-1,3-diyldiimino)diacetate (16)

N,N′-Bis{3-[3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}propane-1,3-diamine

Thioacetic acid (0.06 mL, 0.86 mmol) and $LiOH·H_2O$ (76 mg, 1.81 mmol) were added to a soln of disulfonamide **15** (0.20 g, 0.22 mmol) in DMF (3 mL) and the mixture stirred at r.t. for 1.5 h. The mixture was then diluted with CH_2Cl_2 (40 mL) and washed with sat. $NaHCO_3$ (15 mL). The aqueous layer was again extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with sat. $NaHCO_3$ (20 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude diamine was used without purification.

IR ($CHCl_3$): 3300, 1652, 1602 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61–1.70 (m, 2 H), 1.88–1.98 (m, 4 H), 2.59–2.68 (m, 8 H), 4.05 (t, *J* = 7.0 Hz, 4 H), 5.11 (s, 4 H), 6.00 (t, *J* = 7.0 Hz, 2 H), 6.62 (dd, *J* = 1.4, 7.6 Hz, 2 H), 6.93 (dd, *J* = 1.5, 7.0 Hz, 2 H), 7.31–7.44 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.3, 30.2, 46.2, 47.3, 48.2, 70.6, 104.5, 115.4, 127.2, 127.8, 128.4, 129.1, 136.3, 148.7, 158.1.

Di-*tert*-butyl N,N′-Bis{3-[3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl]propyl}-2,2′-(propane-1,3-diyldiimino)diacetate (16)

K_2CO_3 (0.2 g, 1.45 mmol) and *tert*-butyl bromoacetate (0.17 mL, 1.1 mmol) were added to a soln of the crude diamine (0.16 g, 0.29 mmol) in anhyd MeCN (5 mL) and the mixture stirred at r.t. for 24 h. The solvent was removed under reduced pressure and the residue was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (10 mL). The aqueous layer was again extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc) to provide **16** (0.10 g, 59% from **15**) as a viscous yellow oil.

IR (neat): 2931, 1731, 1653, 1605, 1554 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 18 H), 1.57–1.65 (m, 2 H), 1.87–1.96 (m, 4 H), 2.58–2.62 (m, 8 H), 3.21 (s, 4 H), 4.03 (t, *J* = 7.0 Hz, 4 H), 5.09 (s, 4 H), 5.98 (t, *J* = 7.0 Hz, 2 H), 6.62 (dd, *J* = 1.8, 7.3 Hz, 2 H), 7.01 (dd, *J* = 1.5, 6.7 Hz, 2 H), 7.27–7.44 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4, 26.7, 28.1, 48.0, 51.2, 52.2, 55.5, 70.7, 80.8, 104.3, 115.5, 127.3, 127.8, 128.4, 129.7, 136.4, 148.8, 158.1, 170.7.

Anal. Calcd for $C_{45}H_{60}N_4O_8·0.25CHCl_3$: C, 66.91; H, 7.47; N, 6.90: Found: C, 67.11; H, 7.28; N, 6.74.

N,N′-Bis{3-[3-(hydroxy)-2-oxopyridin-1(2*H*)-yl]propyl}-2,2′-(propane-1,3-diyldiimino)diacetic Acid (17)

Compound **16** (0.28 g, 0.35 mmol) was dissolved in concd HBr–glacial AcOH (1:1, 30 mL) and stirred at r.t. for 5 d. The volatiles were removed under reduced pressure. The residue was washed with EtOAc and Et_2O and dried under high vacuum for 24 h to yield mixed ligand chelator **16** (0.23 g, 81%) as a light-brown hydrobromide salt.

IR (KBr): 3413, 2961, 1741, 1641, 1597, 1547 cm^{-1}.

^{1}H NMR (300 MHz, D_2O): δ = 2.12–2.25 (m, 6 H), 3.27–3.36 (m, 8 H), 4.05–4.10 (m, 8 H), 6.37 (t, *J* = 7.02 Hz, 2 H), 6.96 (dd, *J* = 1.5, 7.6 Hz, 2 H), 7.16 (dd, *J* = 1.5, 6.7 Hz, 2 H).

^{13}C NMR (50 MHz, D_2O): δ = 19.1, 23.6, 46.5, 52.0, 52.1, 53.7, 109.0, 119.0, 129.0, 145.3, 158.6, 168.2.

Anal. Calcd for $C_{23}H_{32}N_4O_8·5HBr·2H_2O$: C, 29.60; H, 4.43; N, 6.00: Found C, 29.47; H, 4.38; N, 5.88.

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