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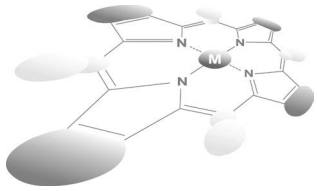

Meso-tetra(dioxanyl)porphyrins: Neutral, low molecular weight, and chiral porphyrins with solubility in aqueous solutions

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Dedicated to Professor Jonathan S. Lindsey on the occasion of his 65th birthday

ABSTRACT: The synthesis of the low-molecular weight, neutral, yet water-soluble porphyrin *meso*-tetra(dioxan-2-yl)porphyrin is described. The key intermediate dioxan-2-carbaldehyde is accessible in either racemic or in stereo-pure forms from commercially available starting materials in three steps. Using 4 × 1 or 2 + 2-type syntheses provide the porphyrin in modest yields. While the racemic aldehyde created an intractable mixture of diastereomers, the enantiopure aldehyde created a single enantiomer of the target porphyrin. The porphyrin was spectroscopically characterized. As its free base or zinc complex, it showed excellent solubility properties in organic and aqueous solvents, though free water-solubility was not achieved. The work expands on the availability of chiral porphyrins and neutral porphyrins with considerable solubility in aqueous solution.

KEYWORDS: *meso*-alkylporphyrins, water-soluble porphyrins, 4 × 1 and 2 + 2-type porphyrin syntheses, water-soluble porphyrins.

INTRODUCTION

The utilization of porphyrins and hydroporphyrins in, for example, cancer photodynamic therapy [1–4], photo-antifungal [5] and -antimicrobials [6], as fluorescence labels [7], fluorescence or photoacoustic imaging agents [4, 8-15], or *in vivo* chemosensors [16, 17] requires their solubility in aqueous biological media. Aqueous solubility is frequently also wanted for their utilization in a number of technical applications, such as (photo)catalysis [18–20] or chemosensing [21]. While water solubility of the porphyrins can be mediated by surfactants or their incorporation into liposomes [22–24], their inherent aqueous solubility is often more practical and thusly more desirable.

Early and effective efforts to impart water-solubility onto *meso*-arylporphyrins, the most commonly used class of fully synthetic porphyrins [25], relied on the introduction of cationic or anionic *meso*-aryl substituents, such as pyridinium-, ammonium-, phosphonate-, sulfonate-, or carboxylate-functionalities [26]. Examples are the classic tetrasulphonated porphyrin **1**, the tetracationic tetrakis-pyridinium porphyrins, but also newer examples, like octacarboxylate **2** (Fig. 1) [27]. These porphyrins are generally prepared *via* Adler-type syntheses of suitably (neutral) precursors, followed by their direct sulfonation, quaternization, or modification with esters and subsequent saponification, respectively.

While successful in generating water-soluble porphyrins, these methods have drawbacks; for instance, the sulfonation reaction condition in particular is harsh. Lindsey and co-workers presented a series of structurally

◊SPP full member in good standing.

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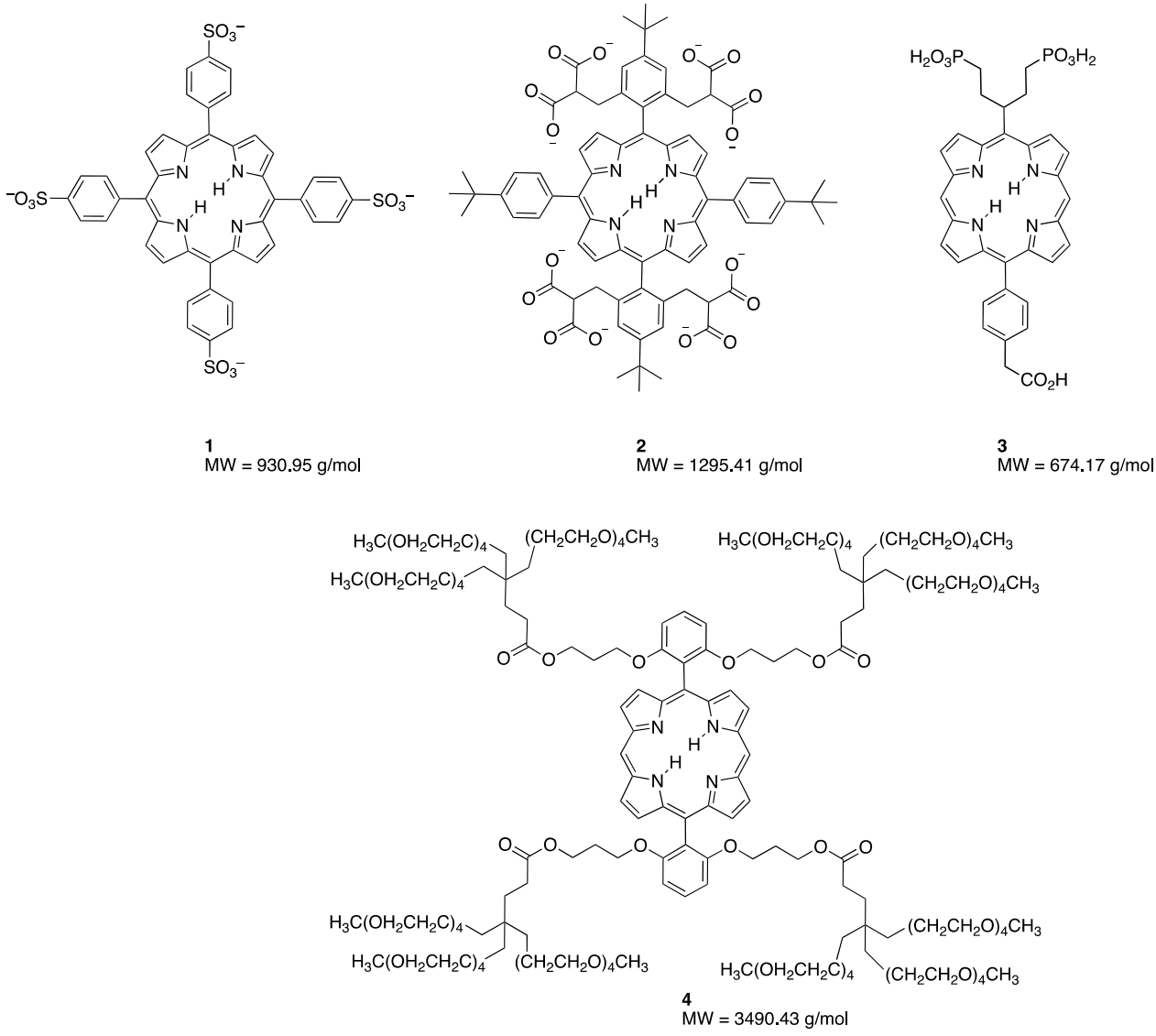


Fig. 1. Examples of literature-known water-soluble porphyrins.

diverse swallowtail porphyrins [28] (and hydroporphyrins [29]) made by total syntheses that elegantly circumvented such harsh post-macrocycle synthesis functional group manipulations to fashion water-soluble derivatives, such as compound **3**, shown to be suitable for bio-conjugation to monoclonal antibodies [30, 31]. We also note the small molecular weight of this compound. However, the chromatographic purification of polyionic porphyrins can be difficult [26].

An alternative method to impart water-solubility into charge-neutral porphyrins late in their synthetic sequence is their conjugation to polyethylene glycols (PEG) moieties [26, 32, 33]. One example among the *meso*-aryl series is PEG-based dendrimer-modified compound **4** [26]. Aqueous media solubility could also be achieved, *inter alia*, by conjugation of the porphyrins to oxygen-rich polar molecules like cyclodextrans [34], (unprotected) sugars [35, 36], or PEGs [26]. However, in order to achieve the high overall oxygen contents needed to achieve water-solubility, their molecular weight increased, often drastically (cf. compound **4**).

The lowest molecular weight porphyrin, archetype porphin $C_{20}H_{14}N_4$, exhibits low solubility in any solvent [37, 38]. *Meso*-substitution, on the other hand, generally is efficient in preventing porphyrin macrocycle π–π aggregation and thusly improving their solubility. This suggests the replacement of the *meso*-aryl groups by small, possibly non-aromatic oxygen/heteroatom-rich entities, such as furanyl- [39, 40], hydropyranyl-, morpholinyl-, or dioxanyl-moieties, *etc*., or even just short PEG chains. Only an astonishingly small number such, and related, systems have been described, among them (water-soluble and unprotected) *meso*-carbohydrate-substituted porphyrins [41–46]. On the

downside, the chemical stability of some pyranosyl-substituted porphyrins was described as being low [41] or the solubility of the hydroxy-protected derivatives in aqueous solution were not specified [46]. Known *meso*-furanyl- [39, 40] and -(1,3-dithian-2-yl)porphyrins [47] are not sufficiently water-soluble. Outside of the patent literature [48], *meso*-dioxanyl-substituted porphyrins have not been described. However, we are also aware that seemingly simple porphyrins may show unexpected solubility or conformational effects [47, 49–51].

This contribution describes our preliminary results on the formation and properties of the 4 • 1 and 2 + 2-type syntheses and aqueous solubility of *meso*-tetra(dioxanyl) porphyrin, a novel small molecular weight porphyrin with considerable solubility in aqueous solution.

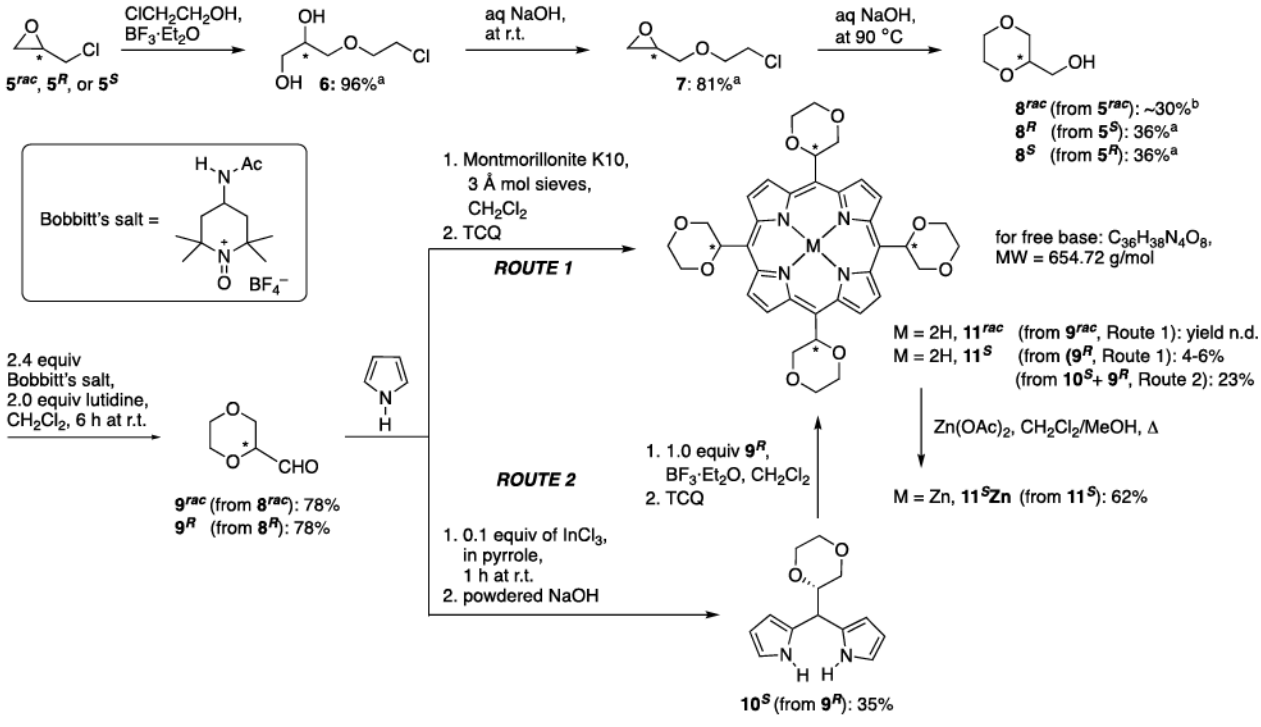
RESULTS AND DISCUSSION

Synthesis of dioxanylaldehyde 9

Crucial starting materials in the syntheses of *meso*-substituted dipyrromethanes, some 2 + 2 syntheses of porphyrins utilizing these dipyrromethanes, and 4 • 1-type syntheses of porphyrins are suitable aldehydes carrying the future *meso*-substituent. A suitable aldehyde, dioxan-2-yl-carbaldehyde **9**, prepared in steps from commercially available racemic epichlorohydrin $\mathbf{5}^{rac}$ (Scheme 1), is known [52]. In short, reaction of epichlorohydrin $\mathbf{5}^{rac}$ with 2-chloroethanol generated the ring opened ether **6** that underwent a base-induced ring-closure to form epoxide $\mathbf{7}^{rac}$. Under more forcing base conditions, it underwent an intramolecular epoxide opening, forming the intermediate alcohol dioxanyl-2-hydroxymethyl $\mathbf{8}^{rac}$ [52, 53]. The final step is the oxidation of the alcohol to the final aldehyde. Instead of the Swern oxidation described by Cushman and co-workers [53], we resorted to an oxidation using an oxoammonium salt (Bobbitt's salt) for the simplicity of this oxidation protocol and the absence of malodorous side products [54, 55]. Most significant in this reaction sequence is the fact that starting from enantiomerically pure (and also commercially available) epichlorohydrins $\mathbf{5}^{S}/\mathbf{5}^{R}$, the enantiomerically pure dioxanylaldehydes $\mathbf{9}^{R}/\mathbf{9}^{S}$, respectively, can also be prepared [53].

4 × 1 Synthesis of *meso*-tetradioxanylporphyrins 11

Reaction of the racemic dioxanylcarbaldehydes $\mathbf{9}^{rac}$ under Adler conditions [56] failed to produce any porphyrin. Under Lindsey conditions [57] (Scheme 1), we retrieved traces of a purple product with a porphyrin-type UV-vis spectrum, the expected composition for the target *meso*-tetradioxanylporphyrin $\mathbf{11}^{rac}$ (as probed by HR-MS, ESI+ mode), but the ^{1}H NMR spectroscopic analyses of this fraction indicated the presence of many products we found intractable. This was attributed to the presence of a host of diastereomers. It was finally decided to simplify the syntheses and abandon the use of the racemic mixture of the aldehyde ($\mathbf{9}^{rac}$).



Scheme 1. Synthetic route toward racemic dioxanylcarbaldehydes **9** from commercially available epichlorohydrins **5** and their conversion along 4 • 1 or 2 + 2-type synthetic routes to title porphyrin **11**. [a] Yield from literature [53]. [b] Yield from literature [52].

Indeed, the use of chiral aldehyde **9**^{R} under Lindsey conditions generated a single isomer of a pink porphyrin **11**^{S} in 2–3% yield (Scheme 1). Balaban and co-workers prepared a range of *meso*-alkylporphyrins using Montmorillonite clay as catalysts in the presence of 3 Å molecular sieves [58]. When these conditions were applied to the chiral aldehyde **9**^{R}, the same pink products **11**^{S} were obtained as a pure fraction possessing identical and porphyrin-like UV-vis spectrum (Fig. 2a) in improved, albeit still modest, yields of 3–6%. Nonetheless, this allowed the preparation of about 40 mg of this porphyrin per batch at a half-gram aldehyde scale. For the characterization of porphyrin **11**^{S}, see below.

2 + 2 Synthesis of *meso*-tetradioxanylporphyrins 10^{S}

The 2 + 2-type syntheses of porphyrins are typically applied for the synthesis of A_2B_2-type systems [59], but it was felt that this approach toward the target A_4-porphyrin could be advantageous. The synthesis of the dipyrromethane building block **10**^{S} from the corresponding enantio-pure aldehyde **9**^{R} under the optimized Lindsey conditions that also avoided any chromatographic workup [60] was straight-forward and yielded the product as an off-white powder in 35% yield (400 mg per 580 mg aldehyde). Its ^{1}H and ^{13}C NMR spectra showed all the diagnostic signals for the pyrrolyl- and dioxanyl-moieties, as well as the hydrogen atom at the central sp^{3}-hybridized carbon atom (for details, see ESI). This dipyrromethene was used without further purification.

A 2 + 2 synthesis using dipyrromethane **10**^{S} and aldehyde **9**^{R} under the standard acid-catalyzed conditions [61, 62] generated the corresponding porphyrin **11**^{S} in 23% yield (Scheme 1). Based on the amount of aldehyde required over the two steps, this yield is only slightly higher than in the best 4 • 1 synthesis of the porphyrin, but the reactions are robust, more readily scalable, and the product porphyrin is readily isolated. No premature decomposition during the handling, zinc insertion (see below), or chromatographic purification of the porphyrin was noticed.

The insertion of the zinc into the free base **11**^{S} proceeded, as expected, under mild and standard conditions [63] (Scheme 1). Metal insertion resulted in the expected changes in the optical spectra of the porphyrin (Fig. 2b). Metal insertion is also indicated by the disappearance of the inner NH proton signals in the ^{1}H NMR of the product (see ESI for details).

Spectroscopic characterization of the *meso*-tetradioxanylporphyrins and its zinc (II) complex

The UV-vis and fluorescence emission spectra of free base dioxanylporphyrin **11**^{S} and its zinc complex **11**^{S}**Zn** in CH_2Cl_2 are, as expected, typical for a porphyrin/metalloporphyrin [64] (Fig. 2, Table 1): Sharp Soret

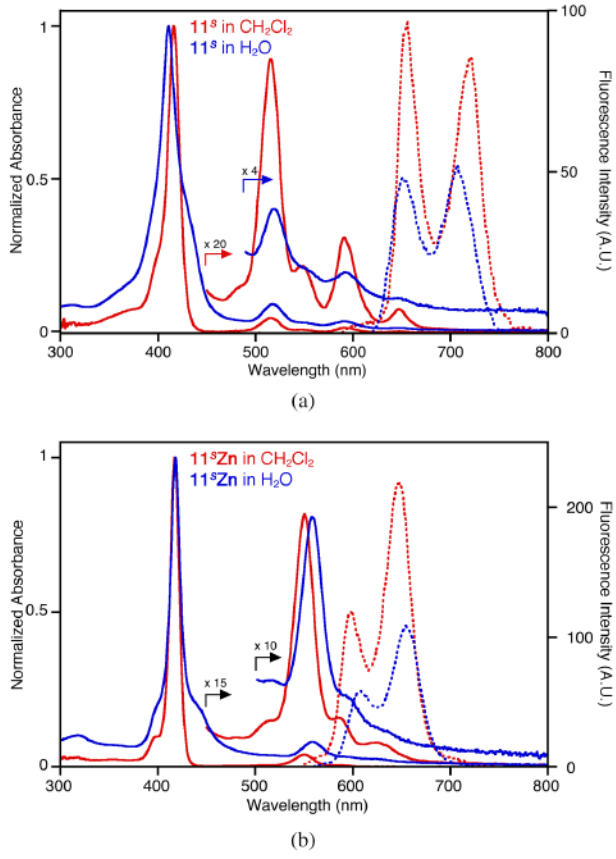


Fig. 2. UV-vis absorption (solid traces) and fluorescence emission spectra (broken traces) of **11**^{S} (A) and **11**^{S}**Zn** (B) in CH_2Cl_2 (red traces) and pure, oxygenated H_2O (blue traces); $\lambda_{excitation} = \lambda_{Soret}$. The multiplication factors listed also reflect the concentration increase.

bands and, for the free base, four Q-bands with the λ_{max} band at 647 nm, and a two-band emission with a small Stoke's shift. The very weak absorbance of the longest wavelength of absorbance was noted at 647 nm. The corresponding peaks of the spectra in H_2O are only slightly shifted, suggesting no major aggregation, although the ratio of the intensity of the Soret band to the side bands is reduced. As could have been expected [31, 65], the fluorescence quantum yield of the compounds in (oxygenated) H_2O is only about 50% of that of the compounds in CH_2Cl_2.

The ^{1}H NMR spectrum of the dioxanylporphyrin **11**^{S} shows the diagnostic signals for a 4-fold symmetric *meso*-substituted porphyrin (Fig. 3): a sharp singlet (at 9.96 ppm, 4H) assigned to the •-protons and the much high-field shifted inner NH proton signal, here at -2.8 ppm (1H). This also suggests the absence of any diastereomers (including atropisomers, at 25°C). Because of the vicinity to the diatropic ring current, all of the dioxanyl protons are much more shifted and better resolved than those in the aldehyde or dipyrromethane (see ESI). Supported by H,H-COSY spectra (see ESI),

Table 1. UV-vis absorption and fluorescence emission peaks and fluorescence quantum yeilds of **11^S** and **11^{S}Zn** in CH_2Cl_2 and H_2O.

Compound	Solvent	UV-vis Absorbance [nm]	Fluorescence Emission [nm]	Fluorescence Quantum Yield
11^S	CH_2Cl_2	416 (Soret), 515, 546 590, 647 nm	656, 720 nm	0.030[a]
11^S	H_2O (air)	415 (Soret), 519, 547, 592, 649 nm	650, 706 nm	0.014[a]
11^{S}Zn	CH_2Cl_2	417 (Soret), 551 nm	598, 648 nm	0.036[b]
11^{S}Zn	H_2O (air)	418 (Soret), 558 nm	654, 610 nm	0.017[b]

[a] *meso*-tetraphenylporphyrin in CH_2Cl_2 used as standard ($\phi = 0.13$); [b] [*meso*-tetraphenylporphyrinato]zinc(II) in CH_2Cl_2 used as standard ($\phi = 0.033$) [66].

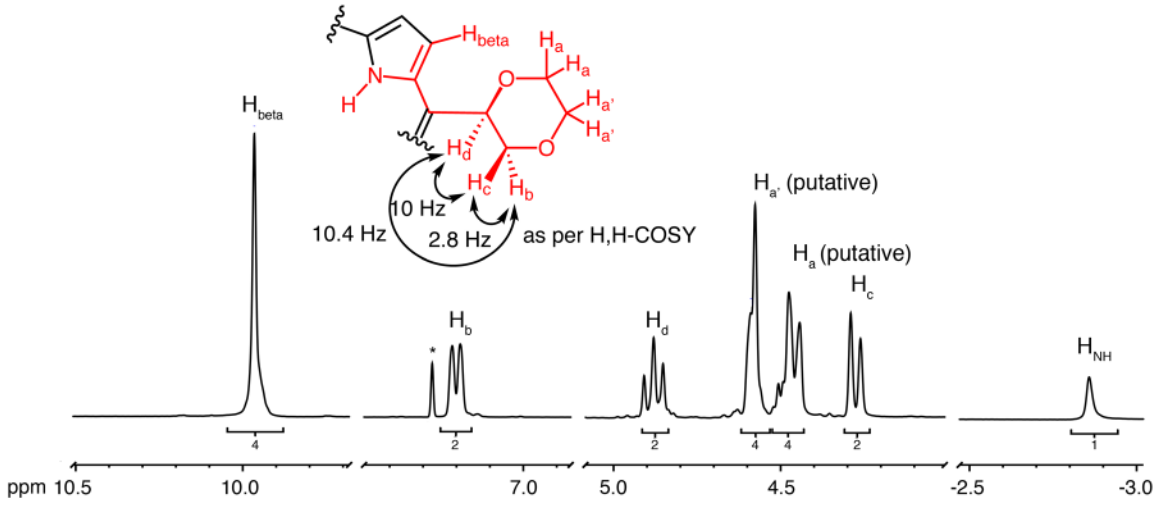


Fig. 3. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *meso*-tetra((*S*)-1,4-dioxanyl)porphyrin **11^S**.

the dd at 4.9 ppm (2H) was assigned to the proton at the *ipso*-carbon, the much-separated d at 7.19 and 4.28 ppm (2H each) to diastereotopic methylene protons at the C3-position, and the two multiplets at 4.58 and 4.45 ppm (4H each) to the two diastereotopic remaining methylene protons (at C5 and C6).

Aqueous solubility of the *meso*-tetradioxanylporphyrins 11^S and 11^{S}Zn

In their solid forms, the *meso*-tetradioxanylporphyrins **11^S** and **11^{S}Zn** do not dissolve in aqueous solutions. But both **11^S** and **11^{S}Zn** readily dissolve in methanol and we successively added aliquots of concentrated (33 and 50 mg/mL, respectively) solutions of the porphyrins in methanol to water to access the solubility in aqueous solutions. Methanol concentration after addition of aliquots was maintained well below 0.2% to avoid its influence on solubility of the porphyrin in water. Using UV-vis spectroscopy, we observed at which concentration we could detect the first signs of turbidity (elevation of baseline) and/or changes in the UV-vis that could indicate aggregation (see ESI). Free base dioxanylporphyrin **11^S** exhibited an aqueous solubility of, conservatively estimated, • than 0.05 mg/mL and likely exceeding 0.1 mg/mL ($1.5 \cdot 10^{-4}$ mol/L) (at which point the aqueous solution contained less than 0.2% MeOH). The corresponding zinc complex proved to be about twice as soluble, with a solubility exceeding > 0.20 mg/mL ($2.8 \cdot 10^{-4}$ mol/L).

CONCLUSIONS

The key aim of this study — the synthesis of a low-molecular weight, neutral, yet water-soluble porphyrin — could be accomplished. Thus, the synthesis of *meso*-tetra(dioxan-2-yl)porphyrin using the key intermediate dioxan-2-carbaldehyde is possible. Unlike the sugar-derived *meso*-pyranose-based porphyrins, however, the synthesis of the title compound did not require any protection group strategies and it is chemically stable. The key intermediate dioxan-2-carbaldehyde can be synthesized in stereoselective fashion from chiral and

commercially available starting materials in steps. The presence of one stereocenter in each *meso*-substituents poses challenges and opportunities. The challenges arise from the creation of a complex mixture of a number of diastereomeric porphyrins upon utilization of a racemic mixture of the aldehyde. The opportunities arise from the ability to generate the enantiomerically pure isomers of the porphyrin, as demonstrated for the tetra-((*S*)-1,4-dioxanyl)porphyrin $\mathbf{11}^{S}$ and its zinc complex $\mathbf{11}^{\mathbf{S}}\mathbf{Zn}$ (though direct evidence of their stereochemical purity was not shown). The neutral products show considerable (for a porphyrin) solubility in aqueous solutions ($1–3 \cdot 10^{-4}$ mol/L range).

The preparation of the enantiomeric analogues to $\mathbf{11}^{R}/\mathbf{11}^{\mathbf{R}}\mathbf{Zn}$, the study of their chiroptic properties, the implications of the ability to readily prepare a pair of enantiomers, the biological uptake of the (chiral) *meso*-tetra(dioxan-2-yl)porphyrins [67], their conversion to the corresponding hydroporphyrins, as well as the synthesis of other porphyrinoids (such as 5,15-disubstituted porphyrins [62], patterned porphyrins [68], or corroles [69]) incorporating the *meso*-dioxan-2-yl groups are currently being pursued in our group.

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Supporting information

A reproduction of the experimental data (such as ^{1}H, ^{13}C NMR spectra, FT-IR, MS spectra, and excitation emission spectra) of all novel compounds described is given in the supplementary material (Figs S1–S21). This material is available free of charge *via* the Internet at https://www.worldscientific.com/doi/suppl/10.1142/S108842462150070X.

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