Host–Guest Systems

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Where is the Oxygen? Structural Analysis of α-Humulene Oxidation Products by the Crystalline Sponge Method**

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Abstract: *Crystal structures of α-humulene, a cyclic sesquiterpene, and its oxidized subproducts, were analyzed by the crystalline sponge method. Regio- and stereochemistry, including absolute configuration when a chiral oxidant was applied, and the stable conformations of all the scaffold-related compounds were successfully determined for samples on a 5–50 μg scale.*

The direct oxidation of nonfunctionalized hydrocarbons is a subject of current interest in synthetic chemistry because of increasing demand for the development of highly efficient, atom-economical synthetic processes.[1] In these reactions however, substrates often carry similar oxidation sites within the molecules and thus the determination of the regio- and stereochemistry arising at the reaction sites is not always easy. The same problems occur in pharmaceutical studies in which drugs are metabolized into oxygenated derivatives.[2] In the case of pharmaceuticals, the structure analysis is even more demanding because, in addition to the need for determining absolute stereochemistry at newly formed stereogenic centers, the analysis must often be carried out with only a trace amount of the products (typically on a microgram scale).

The crystalline sponge method is a recently developed X-ray technique that does not require crystallization of the samples.[3] A porous metal complex absorbs a target molecule into its pores, rendering the target molecule ordered and detectable by X-rays. In this method, it is presumed that the successful structural analysis of one parent compound promises the facile analysis of a series of its derivatives owing to the capture of these derivatives at the same (or better) binding sites in the crystalline sponge. This great advantage is expected to enable us to provide a solution to the question “where is the oxygen?”, a question which researchers often encounter when studying hydrocarbon substrates that are subjected to direct oxidation.

α-Humulene (**1**, Figure 1a) is a cyclic sesquiterpene (formula $C_{15}H_{24}$) with three double bonds and six allylic positions, all of them theoretically able to be oxidized. This unique molecule has previously been used as a precursor for biosynthesis-mimicking natural product synthesis through transannular cyclization.[4] Additionally, there are several reports on the site-selective oxidation of **1** using various oxidation methods.[5] Herein, a series of oxidation products are derived from **1** under various oxidation conditions and all of the products are analyzed using the crystalline sponge method. We show that all of the structural information, including absolute configuration, can be univocally established by single-crystal X-ray analysis using the crystalline sponge method. Our results demonstrate that the crystalline sponge method is a powerful tool for the structural analysis of

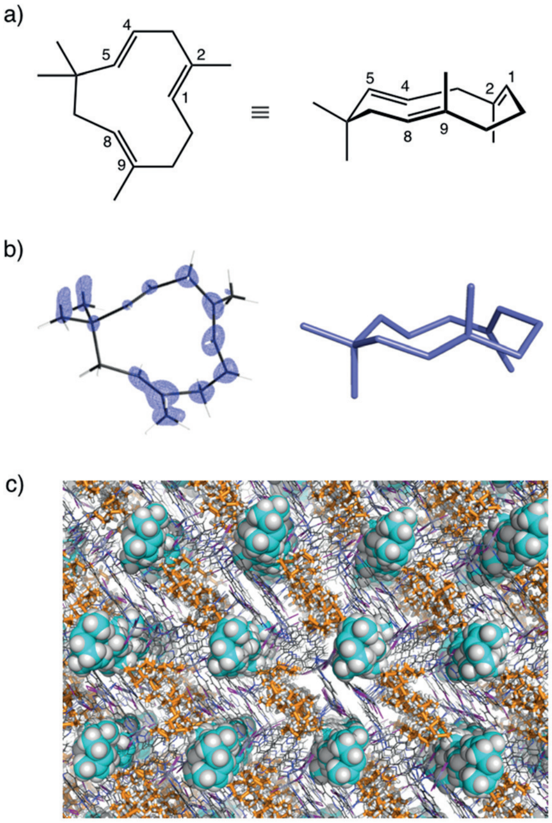

Figure 1. Structure determination of α-humulene by the crystalline sponge method. a) Structure of **1**; b) Superimposition of the F_o-map ($\sigma = 0.5$) and the X-ray crystal structure (left), and side view of the X-ray structure (right); c) X-ray structure of crystalline sponge **2·1**. In (c), the host framework is given as a light-gray stick model, **1** is shown in blue as a space-filling model, and cyclohexane molecules are shown as an orange stick model.

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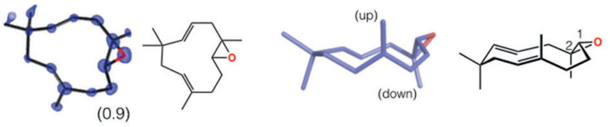
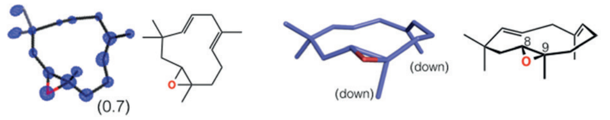
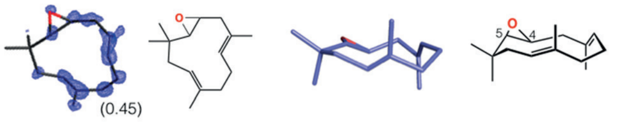
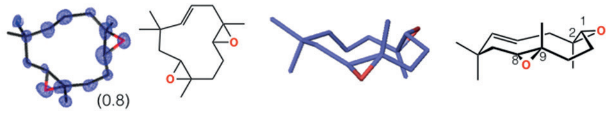
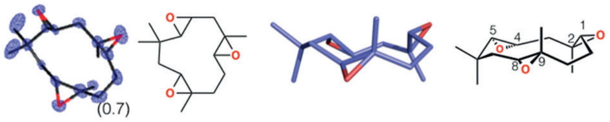
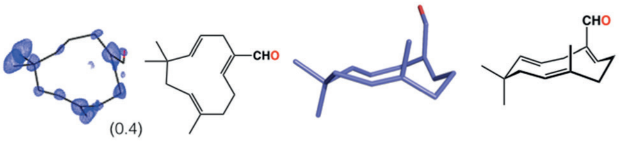
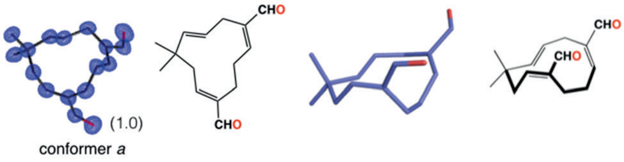
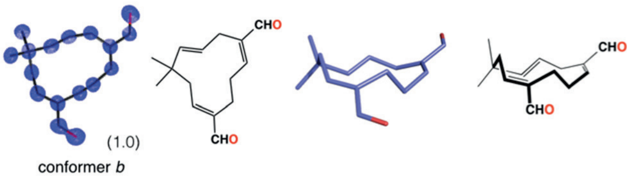
a series of oxidized derivatives from a parent molecule, and will be useful in total synthesis as well as in drug discovery.

Throughout the study, network complex [(ZnI$_2$)$_3$-(tpt)$_2$·x(cyclohexane)]$_n$ (**2**; tpt = 1,3,5-tris(4-pyridyl)triazine) was used as the crystalline sponge.[6] First, parent compound **1** was analyzed. A tiny crystal of **2** (230 × 170 × 80 μm) was treated with a small amount of **1** (5 μg) dissolved in cyclohexane (5 μL) in a capped, pierced vial at 50 °C for 2 d to give a guest-absorbed crystal (**2·1**), which was investigated by X-ray diffraction.[7] Because of the presence of three *E*-configured double bonds in the cyclic scaffold, **1** is expected to adopt a rigid conformation. However, apart from an Ag$^+$–**1** adduct,[5c] the native conformation of **1** has never been analyzed by crystallography because it is an oil at around room temperature. The crystallographic analysis of the **2·1** complex clearly showed the inclusion of one molecule of **1** per asymmetric unit within the pores of the network along with disordered cyclohexane molecules (Figure 1 b,c). The three *E*-configured double bonds are perpendicular to the cyclic framework, and this pushes the 2- and 9-methyl groups down and up, respectively, in good agreement with the Ag$^+$–**1** structure[5c] as well as with the computer-simulated stable conformation of **1**.[8] This coincidence explains the conformational rigidity of **1** as the guest conformation in the sponge pores is often influenced by host–guest interactions and is not always the most stable. Note that conformationally fixed cyclic *E*-alkenes are chiral; 1R_p*, 4S_p*, and 8R_p* relative planar chirality is defined for the three *E*-configured double bonds. Thus, in this case, the crystalline sponge method clearly revealed both the chemical structure and the most stable conformation of **1**.

With satisfactory X-ray data for parent molecule **1** in hand, we synthesized several oxidized derivatives of **1** to examine whether the same scaffolds could fit into the pores of the crystalline sponge after oxidation. When **1** was oxidized with one equivalent of *m*-CPBA (*meta*-chloroperbenzoic acid) in CHCl$_3$ at −10 °C, three major components were formed and isolated in a ratio of circa 80:15:5 (Table 1, entry 1). Each component has a molecular formula of C$_{15}$H$_{24}$O according to mass spectrometric measurements. These products are expected to be three regioisomeric monoepoxides with different oxidation sites. However, specifying the reaction site and especially elucidating the most stable conformation of each product is difficult using only NMR spectroscopic analysis. These structural concerns were easily addressed with the crystalline sponge method. After column chromatographic separation, the three components

Table 1: Preparation and crystallographic analysis of α-humulene oxidation products.

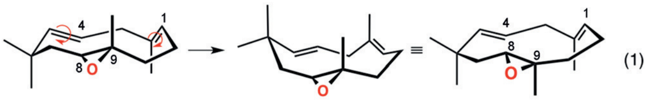
Entry	Conditions	Products (Yields [%])	Crystal structures[a]
1[b]	*m*-CPBA (1.0 equiv) CHCl$_3$ -10°C to RT, 15 h	**3** (75)	
		4 (14)	
		5 (5)	
2	*m*-CPBA (2.0 equiv) CHCl$_3$ -10°C to RT, 15 h	**6** (30)	
3	*m*-CPBA (3.5 equiv) CHCl$_3$ -10°C to RT, 15 h	**7** (52)	
4[c]	SeO$_2$ (1.0 equiv) *t*BuOH reflux, 24 h	**8** (15)	
5[d]	SeO$_2$ (3.0 equiv) *t*BuOH reflux, 24 h	**9** (36)	 

[a] Left: Wire framework presentation overlaid with F_o maps. Values in parentheses are σ levels. Right: Stick presentation. [b] A mixture of **3**–**5** was obtained. [c] See the discussion in the text and the Supporting Information. [d] Two conformers *a* and *b* are found in the crystal structure.

were treated with crystalline sponge **2** and the guest-absorbed crystals were subjected to single-crystal X-ray analysis.

The crystallographic analysis showed the major product (isolated in 75% yield) to be (1*R**,2*R**)-1,2-epoxy humulene (**3**; Table 1, entry 1). In the crystallographic analysis, one molecule of **3** (occupancy 48%; the position is shared with a disordered cyclohexane molecule (occupancy 52%)) was refined.[9] Four disordered solvent molecules fill the remaining pore voids. The conformation of the cyclic scaffold of **3** is the same as that of parent **1** with $4S_p$* and $8R_p$* configurations. In this conformer, the epoxy oxygen is located outside of the cyclic framework. Selective formation of this conformer is explained by the *exo* attack of *m*-CPBA on the 1,2-double bond of **1**.

The second product (14%) was determined to be 8,9-epoxidized **4** (for convenience, scaffold carbons are numbered using the same scheme as those of parent **1** throughout this study).[10] Interestingly, the 9-methyl group of **4** is pointed downward and thus the observed conformation of the 11-membered cycle is diastereomeric to that of **1**. Presumably, the initial product is *exo*-attacked **4′**, and this turns into conformer **4** by flipping of the two double bonds [Eq. (1)]. The observed (and presumably the most stable) conformation has $1S_p$*$4R_p$* planar chirality for the two double bonds and 8*R**9*R** central chirality for the epoxy carbons. The third component (5%) was identified as the 4,5-epoxidized compound (**5**), a stable conformer with $1S_p$*$8R_p$* planar chirality and 4*S**5*S** central chirality.[11]



(1)

4′ **4** (enantiomeric to the left)

It is noteworthy that the binding sites of the epoxide moieties are substantially different for **3**, **4**, and **5**, despite their closely related scaffold and functional groups. Compounds **3** and **4** are involved in hydrogen bonding with the network and are placed at better binding sites: the oxygen atom of **3** forms two −CH⋯O bonds with two β −CH moieties of two adjacent pyridine moieties of a tpt ligand in the network structure; **4** is maintained by two −CH⋯O bonds between the two α and β −CH units of one pyridyl group of a tpt core and the epoxide oxygen atom. Compound **5** is not hydrogen bonded with the host framework.

Upon oxidation of **1** with two equivalents of *m*-CPBA, a single isomer of the diepoxide with a formula of $C_{15}H_{24}O_2$ (based on mass spectrometric measurements) was isolated (Table 1, entry 2). In addition to the regioselectivity, we were also interested in determining the relative stereochemistry between the two epoxide moieties, but this is very difficult using only spectroscopy. The stereochemical issues can only be addressed by crystallography. After purification by recrystallization, major product **6** was treated with crystalline sponge **2** and the guest-absorbed crystal was subjected to X-ray diffraction.[12] The crystallographic analysis showed the reaction sites to be the 1,2- and 8,9-olefinic parts of **6** and the relative stereochemistry to be 1*R**2*R**8*S**9*S**. The relative planar chirality on the 4,5-olefinic moiety was R^*_p. Furthermore, triepoxide **7** with three *exo*-epoxy oxygen atoms was isolated as a major product when 3.5 equiv of *m*-CPBA were applied (Table 1, entry 3). The scaffold conformations of both diepoxide **6** and triepoxide **7** were the same as that of parent **1**.[13]

The six allylic carbons in **1** are also theoretically active toward oxidation. We studied the site selectivity in SeO_2 oxidation by the crystalline sponge method and observed that addition of SeO_2 (1.0 equiv) to a solution of **1** in refluxing *t*BuOH provided allylic aldehyde **8** in 15% yield (Table 1, entry 4). The other aldehydes or alcohols that could result from oxidation at different reaction sites were not isolated. In the crystallographic analysis, despite a good R_1 value (0.0397), unnatural bond lengths and angles were detected for the guest framework because of low guest occupancy and the thermal motion of the guest, and we could only elucidate a rough molecular framework for the guest. Nevertheless, oxidation at the 2-methyl group was strongly suggested by the new appearance of an electron-density peak, assignable as a formyl oxygen, near the 2-methyl carbon (C−O distance = 1.39(6) Å; see the Supporting Information).[14]

Dialdehyde **9** was obtained in 36% yield when 3.0 equiv of SeO_2 were applied to **1** (Table 1, entry 5).[15] In the crystallographic analysis, two conformers (*a* and *b*) of **9** are found in the asymmetric unit. Surprisingly, the molecular structure of both conformers revealed that the *E* configurations of the C1=C2 and C8=C9 double bonds were inverted to the opposite configurations in the isolated product. The isomerization may take place via bond rotation in the SeO_2–ene reaction intermediate, in which the double bond is temporarily lost. The *E*/*Z* stereochemistry of trisubstituted olefins is in general hard to determine by NMR spectroscopy, yet can be easily visualized by crystallography. This example further demonstrates the great potential of the crystalline sponge method for the full determination of the stereochemistry of the target molecules.

Finally, we applied our method to the absolute structure determination of chiral humulene mono- and diepoxides prepared with a chiral oxidation reagent. Using the asymmetric epoxidation conditions of Shi and co-workers with sugar derivative **10** (33 mol%) and oxone (1.1 equiv) as co-oxidant in a buffered solution at −10 °C, monoepoxide **3** was obtained in 41% yield.[16] Analysis by HPLC on a chiral stationary phase showed the enantiomeric excess of **3** to be 85%. Thus-obtained **3** (85% *ee*) was included within the crystalline sponge and the guest-soaked network structure was crystallographically analyzed. As a result of the host–guest interaction with the chiral guest, the network was distorted in a chiral manner and the space group *C*2/*c* became *C*2. The anomalous scattering from the host iodine atoms allowed us to speculate the absolute structure of **3** to be 1*R*,2*R* (Flack parameter = 0.215(13)).[17] Upon treatment of **1** with **10** (3.2 equiv) and oxone (5 equiv) at −10 °C, we obtained a mixture of two diepoxides (circa 50% yield, obtained in a 1:1 ratio as determined by NMR spectroscopy). From this mixture, we isolated two major isomers, diepoxide **6** and its diastereomer **11** with *ee* values of 40% and more than 99%, respectively (Figure 2a). The absolute structure of **11** was

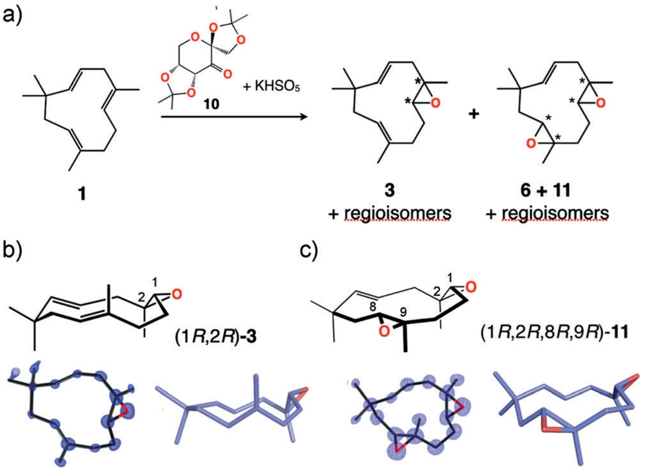


Figure 2. Asymmetric epoxidation of α-humulene **1**. a) Reaction scheme. b,c) Crystal structures of b) (1*R*,2*R*)-**3** and c) (1*R*,2*R*,8*R*,9*R*)-**11**. For the bottom structures in (b) and (c), the left images show the superimposition of the F_o-map and the X-ray structure and the right images show the side view of the X-ray structure. Atom colors: C = blue; O = red.

determined to be 1*R*,2*R*,8*R*,9*R* with Flack parameter = 0.092(11)[18] (Figure 2c). We did not try to determine the absolute structure of diastereomer **6** because of its low *ee* value.

In summary, all the structures of the oxidation products of parent compound **1**, including their relative and absolute stereochemical configurations, were successfully determined using the crystalline sponge method. All the measurements were performed with only microgram quantities of the compounds. These experiments brought us not only structural information but also several lessons on using the crystalline sponge method for analysis. First, we clearly demonstrated that if a parent compound fits the sponge pore, its scaffold-related derivatives are also likely to be good substrates. Second, we found that the guest-binding site for the derivatives may be different from that of the original molecule if the derivatives find better binding sites as a result of additional host–guest interactions in the pore (for example, by hydrogen bonding with the host framework). Third, it is clear that careful consideration is necessary when discussing stable conformations based on these crystal structures because the guest conformation is biased by host–guest interactions in the crystalline sponge. Our method can provide highly valuable information on incorporated molecular scaffolds, such as functional group position, stereochemistry, and the 3D molecular arrangement. We expect that the crystalline sponge method, even considering its limitations, will significantly accelerate both synthetic research and drug discovery.

Experimental Section

General procedure for *m*-CPBA epoxidation: *m*-CPBA (1–3.5 equiv) was added portionwise to a solution of **1** in $CHCl_3$ (circa 0.1 M) maintained at −10 °C. After 10 h at −10 °C, the mixture was allowed to reach RT over 5 h. After addition of pentane, washing with H_2O, and evaporation to dryness, the products were purified using SiO_2/$AgNO_3$-SiO_2 column chromatography for **3**, **4**, and **5**, and by recrystallization from petroleum ether for **6** and **7**.

General procedure for SeO_2 oxidation: SeO_2 (1–3 equiv) was added portionwise to a solution of **1** in *t*BuOH (circa 0.2 M) and the solution was refluxed for 1 day. The resulting mixture was filtered, extracted using cyclohexane and washed with H_2O several times, dried, and evaporated to dryness. Column chromatography and preparative TLC (SiO_2, cyclohexane/AcOEt) afforded aldehydes **8** and **9**.

General procedure for chiral epoxidation: Two aqueous solutions of oxone (1–5 equiv) and K_2CO_3 were added dropwise and simultaneously at −10 °C over 2 h to a flask charged with **1**, Shi's catalyst (0.33–3.2 equiv), Bu_4NHSO_4 (0.1 equiv), CH_3CN/$MeOCH_2OMe$ (1:2 ratio) and an aqueous solution of $Na_2B_4O_7$/Na_2EDTA (Na_2EDTA = disodium ethylenediaminetetraacetate). At the end of the addition, the flask was allowed to stand at −10 °C for 1 h. Cyclohexane was added, the mixture was filtered, and the phases were separated. After extractions, drying, and evaporation to dryness, successive column chromatographies (SiO_2/$AgNO_3$-SiO_2, cyclohexane/AcOEt) and recrystallizations (MeOH/H_2O) yielded epoxides $\mathbf{3}^*$, $\mathbf{6}^*$, and $\mathbf{11}^*$.

General procedure for guest inclusion into crystalline sponge: To a micro vial containing a piece of single crystal of **1** and cyclohexane (45 μL) was added 5–50 μL of a cyclohexane solution of the target compound (1 mg/1 mL). Then, the micro vial was allowed to stand at 5–50 °C and the solvent was gradually evaporated over 2–7 d, according to a previously reported procedure.[3a,b] For details, see the Supporting Information.

X-ray crystallographic analysis: The guest-included crystalline sponges were subjected to single-crystal X-ray diffraction. All the data were collected using MoKα (λ = 0.71073 Å) or CuKα X-ray radiation (λ = 1.54184 Å). All crystal structures were solved using SHELXT[19] and refined using SHELXL.[20] For compounds **3**, **6** (one of two independent molecules), **7**, **9**, and $\mathbf{11}^*$, no restraints were applied for the guest frameworks. For compounds **1**, **4**, **5**, **6** (the other independent molecule), **8**, and $\mathbf{3}^*$, minimum numbers of restraints (SIMU, DFIX, and/or SAME) were applied. Highly disordered solvent molecules were refined by appropriately applying restraints (DFIX, DANG, SIMU, and ISOR).

Keywords: configuration determination · crystalline sponge · host–guest systems · sesquiterpenes · structure elucidation

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[7] Crystallographic data for **2·1**: $C_{58.04}H_{65.65}I_6N_{12}Zn_3$ $M = 1888.83$, monoclinic *C2/c*, $a = 34.7408(7)$, $b = 14.9018(2)$, $c = 31.0584(7)$ Å, $\beta = 101.437(2)°$, $V = 15759.7(5)$ Å^3, $Z = 8$, $D_{calc} = 1.592$ g cm^{-3}, GoF = 1.052, $R_1 = 0.0539$, and $wR_2 = 0.1789$. CCDC-1053230 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[9] Crystallographic data for **2·3**: $C_{67.35}H_{83.80}I_6N_{12}O_{0.48}Zn_3$ $M = 2026.70$, monoclinic *C2/c*, $a = 34.5900(4)$, $b = 14.92734(18)$, $c = 30.1552(5)$ Å, $\beta = 100.9231(13)°$, $V = 15288.1(4)$ Å^3, $Z = 8$, $D_{calc} = 1.761$ g cm^{-3}, GoF = 1.072, $R_1 = 0.0528$, and $wR_2 = 0.1592$. CCDC number: 1053227.

[10] Crystallographic data for **2·4**: $C_{58.08}H_{62.94}I_6N_{12}O_{1.45}Zn_3$ $M = 1909.79$, monoclinic *C2/c*, $a = 34.9245(6)$, $b = 14.9263(2)$, $c = 29.7839(5)$ Å, $\beta = 101.228(2)°$, $V = 15229.0(4)$ Å^3, $Z = 8$, $D_{calc} = 1.666$ g cm^{-3}, GoF = 1.074, $R_1 = 0.0556$, and $wR_2 = 0.1807$. CCDC number: 1053228.

[11] Crystallographic data for **2·5**: $C_{57.60}H_{63.36}I_6N_{12}O_{0.59}Zn_3$ $M = 1890.76$, monoclinic *C2/c*, $a = 34.9032(8)$, $b = 14.8011(2)$, $c = 31.0811(7)$ Å, $\beta = 101.564(2)°$, $V = 15730.7(6)$ Å^3, $Z = 8$, $D_{calc} = 1.597$ g cm^{-3}, GoF = 1.063, $R_1 = 0.0606$, and $wR_2 = 0.1964$. CCDC number: 1053229.

[12] Crystallographic data for **2·6**: $C_{60}H_{66}I_6N_{12}O_2Zn_3$ $M = 1944.75$, monoclinic *C2/c*, $a = 34.8531(7)$, $b = 14.7838(3)$, $c = 31.0339(8)$ Å, $\beta = 101.296(2)°$, $V = 15680.8(6)$ Å^3, $Z = 8$, $D_{calc} = 1.648$ g cm^{-3}, GoF = 1.045, $R_1 = 0.0624$, and $wR_2 = 0.2055$. CCDC number: 1053226.

[13] Crystallographic data for **2·7**: $C_{67.04}H_{82.49}I_{6.03}N_{12}O_{1.35}Zn_{3.02}$ $M = 2040.22$, monoclinic *C2/c*, $a = 34.651(4)$, $b = 14.9888(15)$, $c = 30.113(3)$ Å, $\beta = 100.7353(19)°$, $V = 15366(3)$ Å^3, $Z = 8$, $D_{calc} = 1.764$ g cm^{-3}, GoF = 1.041, $R_1 = 0.0436$, and $wR_2 = 0.1427$. CCDC number: 1053231.

[14] Crystallographic data for **2·8**: $C_{66.18}H_{81.06}I_{6.04}N_{12}O_{0.41}Zn_{3.02}$ $M = 2014.90$, monoclinic *C2/c*, $a = 34.7076(8)$, $b = 15.0136(4)$, $c = 29.9475(8)$ Å, $\beta = 100.783(2)°$, $V = 15329.7(7)$ Å^3, $Z = 8$, $D_{calc} = 1.746$ g cm^{-3}, GoF = 1.025, $R_1 = 0.0397$, and $wR_2 = 0.1100$. CCDC number: 1053222.

[15] Crystallographic data for **2·9**: $C_{75}H_{82}I_6N_{12}O_4Zn_3$ $M = 2173.03$, monoclinic *C2/c*, $a = 34.307(7)$, $b = 14.392(3)$, $c = 34.931(7)$ Å, $\beta = 106.22(3)°$, $V = 16560(6)$ Å^3, $Z = 8$, $D_{calc} = 1.743$ g cm^{-3}, GoF = 1.064, $R_1 = 0.0725$, and $wR_2 = 0.2268$. CCDC number: 1053225.

[16] Z.-X. Wang, L. Shu, M. Frohn, Y. Tu, Y. Shi, *Org. Synth.* **2003**, 9 – 17.

[17] Crystallographic data for **2·3***: $C_{110.55}H_{118.45}I_{11.68}N_{24}OZn_6$ $M = 3673.11$, monoclinic *C*2, $a = 34.5793(12)$, $b = 14.9292(5)$, $c = 30.6203(11)$ Å, $\beta = 101.179(7)°$, $V = 15507.5(10)$ Å^3, $Z = 4$, $D_{calc} = 1.573$ g cm^{-3}, GoF = 0.998, $R_1 = 0.0523$, and $wR_2 = 0.1680$, Flack (Parsons) = 0.215(13). This Flack parameter value is below the IUCr regulation criteria (0.3), but is not sufficient to fully convince the absolute stereochemistry. The 1*R*,2*R* configuration of **3*** was thus confirmed by converting it into **11*** whose configuration was determined with a reasonable Flack parameter (see Ref. [19] and the Supporting Information). CCDC number: 1053224.

[18] Crystallographic data for **2·11***: $C_{105}H_{108}I_{12}N_{24}O_2Zn_6$ $M = 3653.17$, monoclinic *C*2, $a = 34.814(3)$, $b = 14.9103(11)$, $c = 30.057(3)$ Å, $\beta = 101.500(2)°$, $V = 15289(2)$ Å^3, $Z = 4$, $D_{calc} = 1.587$ g cm^{-3}, GoF = 1.046, $R_1 = 0.0483$, and $wR_2 = 0.1568$, Flack (Parsons) = 0.092(11). CCDC number: 1053223.

[19] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2015**, *71*, 3 – 8.

[20] G. M. Sheldrick, *Acta Crystallogr. Sect. C* **2015**, *71*, 3 – 8.

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