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Synthesis of an Alleged Byproduct Precursor in Iodixanol Preparation

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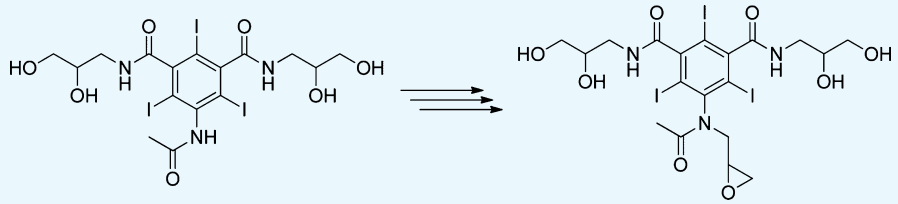
Supporting Information



ABSTRACT: N^1,N^3-Bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(*N*-(oxiran-2-ylmethyl)acetamido)isophthalamide (**1**), the alleged precursor of several minor byproducts formed when the X-ray contrast agent iodixanol is synthesized from 5-acetamido-N^1,N^3-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide (**2**), has been successfully prepared with an overall yield of 25%. Epoxide **1** enabled the confirmation of its presence in the reaction mixture during the preparation of iodixanol when amide **2** was used as the starting material.

1. INTRODUCTION

Fully understanding an industrial process is of great importance when process improvements are to be made.[1] Small quantities of byproducts formed in a reaction, which on a laboratory scale synthesis are neglectable, become important to minimize when the reaction takes place on a ton-scale on a daily basis. From an industrial perspective, it is therefore important to fully understand how byproducts are formed in a given process. With such knowledge in hand, it could be possible to alter the reaction conditions to diminish the byproduct formation, or even better, remove them totally.

X-ray-contrast agent iodixanol (Figure 1) can be prepared by several methods.[2−4] If amide **2** is used as the starting material under basic conditions, its anion would react with epichlorohydrin, a reagent in the reaction, to give epoxide **1** as an intermediate in a two-step process. Because of the reactive nature of epoxides,[5] and the presence of several nucleophilic sites in amide **2**, epoxide **1** could potentially be a precursor for the formation of several minor byproducts in addition to the major and desired product iodixanol.

Previous results have shown that amide **2** is present in two anionic forms, compounds **2a** and **2b** (Figure 2a), upon treatment with base where anion **2a** is the dominating species.[6] Anion **2b** can react with epoxide **1**, which results in the formation of the imidate byproduct depicted in Figure 2b. The formation of the imidate has previously been proved experimentally.[6] Another plausible pathway to this product could be via the intermediate, as shown in Figure 2c. This byproduct and other byproducts[1] are then removed from crude iodixanol during work-up and purification processes, resulting in pure iodixanol.

Epoxide **1** is expected to have a short lifetime under the reaction conditions, and its isolation from the reaction mixture is therefore not a viable option when substantial amount of material is needed for reactivity studies and for studies directed toward elucidating its role in byproduct formation. Herein, we communicate our synthetic approach for the preparation of epoxide **1**, which also allowed us to confirm its presence in small amounts during iodixanol synthesis when amide **2** is used as starting material.

2. RESULTS AND DISCUSSION

2.1. Synthesis. Initially, we attempted a protection group-free synthesis of epoxide **1** by performing a regioselective N-alkylation[7] of the acetamide moiety within substrate **2**, followed by a direct epoxidation of the resulting alkene by a Prileschajew reaction.[5] However, to our disappointment, we quickly ended up with solubility problems of the material under solvent conditions required to conduct the necessary synthetic transformations. To get around the solubility issue, protection of the free hydroxyl groups was inevitable.

Substrate **2** was therefore converted to the *tert*-butyl(dimethyl)silyl (TBS)-protected product **3** in 96% yield, utilizing standard reaction conditions (Scheme 1).[8] The TBS protection group was thought to be suitable for the chemistry required for the formation of epoxide **1** and, at the same time, to be relatively easy to remove in the final step, utilizing a global deprotection strategy. Silyl ether **3** was then subjected to

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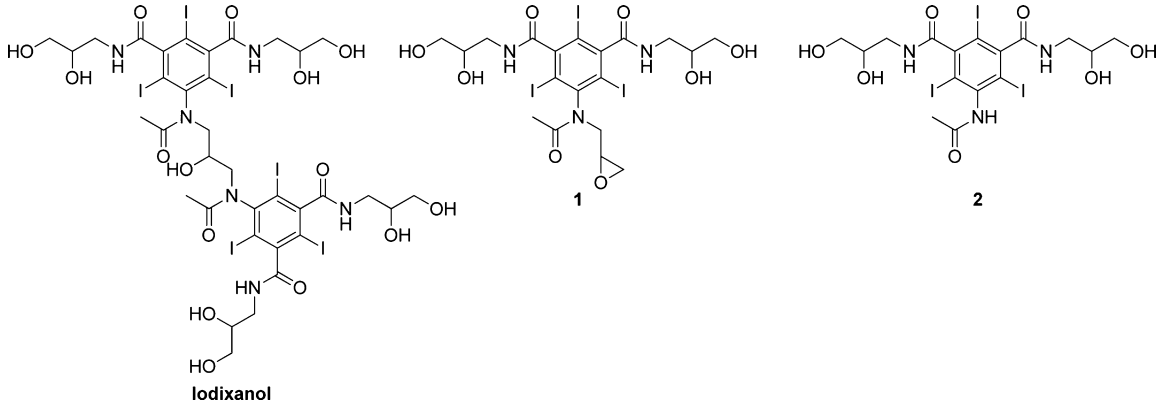

Figure 1. Structure of iodixanol, epoxide **1**, and amide **2**.

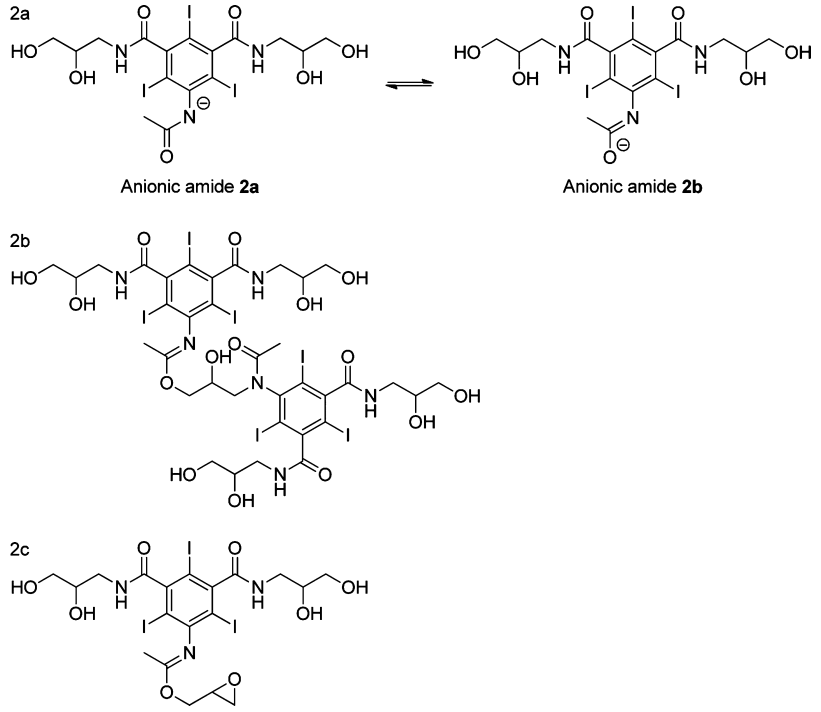

Figure 2. (a) Two anionic forms of amide **2**; (b) byproduct formed if epoxide **1** reacts with the anionic form of amide **2**; and (c) potential intermediate from the reaction between anionic amide **2** and epichlorohydrin.

a regioselective N-alkylation of the acetamide, resulting in the formation of the desired alkene **4** in 90% isolated yield.

Attempts to convert substrate **4** directly to epoxide **7** upon oxidation by *m*-CPBA in a range of solvents[9] and with hydrogen peroxide in glycine buffer[10] were all unsuccessful. A more labor-intensive route was therefore required to prepare the target epoxide. Thus, alkene **4** was subjected to an Upjohn dihydroxylation in acetone/water (6:1) resulting in a clean conversion to the corresponding diol **5** (96% yield).[11−13]

Treating glycol **5** with methanesulfonyl chloride (MsCl) under conditions described by O'Donnel and Burke[14] gave predominant mesylation of the primary hydroxyl group, resulting in the isolation of mesylate **6** in 73% yield. In addition, 10% of the product resulting from mesylation of both hydroxyl groups (compound **8** in Scheme 1) was isolated from the reaction. The ^{1}H and ^{13}C NMR chemical-shifts for the mesyl groups in compounds **6** and **8** were in good agreement with literature reports for similar compounds.[14−16] Treating compound **6** with 2 M NaOH (aq) in ether at room temperature, according to the Izuhara and Katoh procedure,[17] resulted in the formation of epoxide **7** (70% isolated yield) over the course of 1 h. Finally, subjecting substrate **7** to tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) at room temperature gave target compound **1** in 86% isolated yield after a tedious purification process,[18] which involved three rounds of flash chromatography to fully remove all salt from the product. Attempts to remove salts and excess TBAF from the product by using a mix of mildly acidic Ca^{2+} and basic ion-exchange resins were only partly successful,[19] and unfortunately also resulted in significant loss of product.

Epoxide **1** was found to be stable under neutral conditions and when stored neat. However, when exposed to acidic conditions, the epoxide underwent ring opening readily. Comparing the high-performance liquid chromatography (HPLC) chromatograms of compound **1** prepared herein and the reaction mixture during industrial production of iodixanol enabled us to confirm that epoxide **1** was indeed present in small quantities during the preparation of iodixanol

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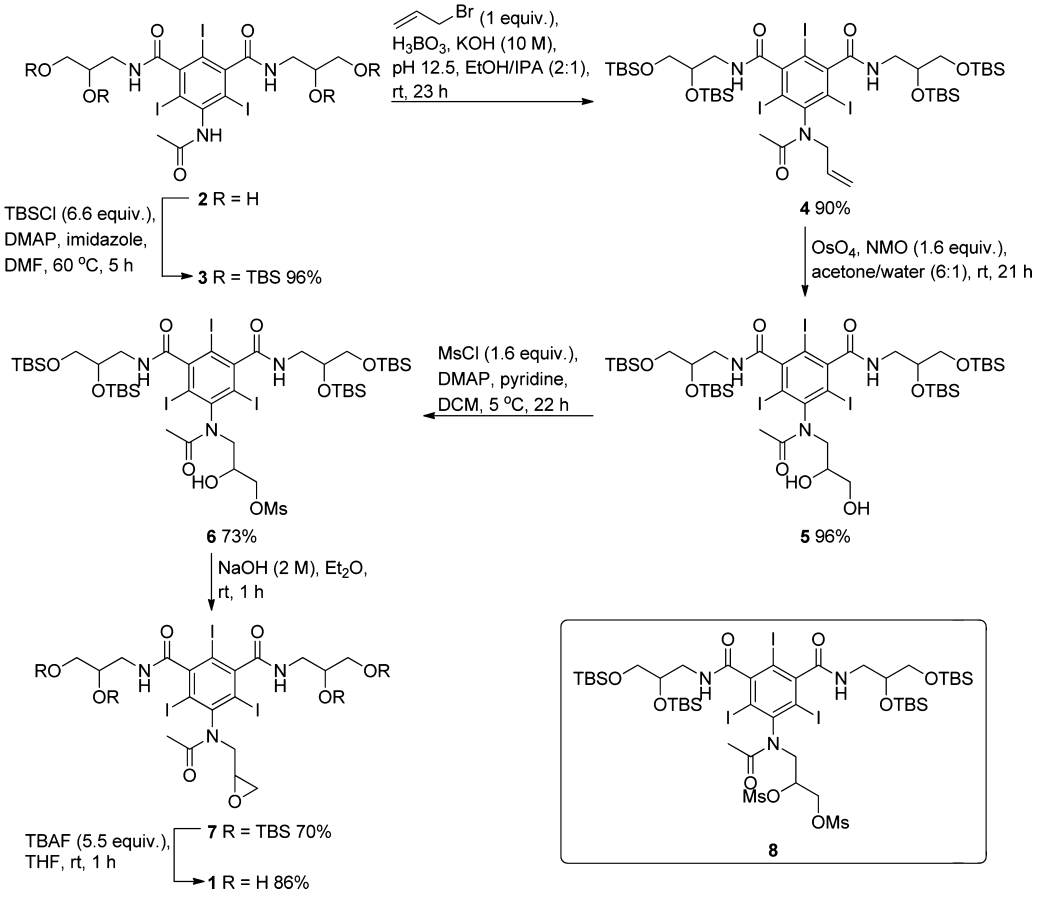
Scheme 1. Synthetic Pathway toward Epoxide 1



(see Figures S1 and S2 in the Supporting Information), thus opening up for potentially being the precursor of byproducts formed during production. Interestingly, we also found that epoxide **1** partly ring-opens to iohexol (Figure 3) on the analytical HPLC column.

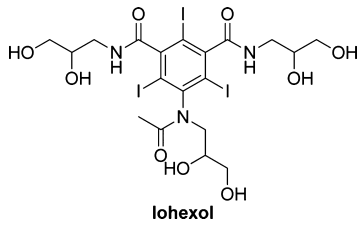


Figure 3. Structure of iohexol.

2.2. Rotational Conformation. The predominant rotational conformation of the acetamide bond CO−N in compounds **2** and **3** was in the endo-form, where the carbonyl moiety is directed toward the ring, as shown in Figure 4.[20] However, the most favored rotational isomer of the alkylated acetamide in compounds **4**−**7** and **1** was the exo-form. The exo-conformation is also the dominating species in iohexol, where the acetamide is alkylated.[21] Isomerism of all compounds was determined by the split acetyl signal in ^{1}H NMR into one major and one minor peak, with the endo-peak positioned downfield of the exo-peak, because of ring-current effects.[22] For compound **3**, the endo-/exo-peaks were positioned at chemical shifts 2.01 and 1.58 ppm in a 27:1 ratio, respectively, and the equivalent peaks for compound **4** were located at 2.18 and 1.73 ppm in a 1:20 ratio (see Figure S3 in the Supporting Information).

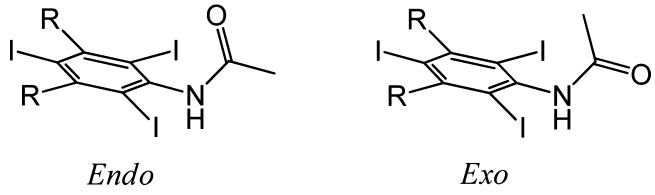


Figure 4. Endo-/exo-isomerism of the acetamide attached to the triiodinated benzene ring.

^{1}H NMR analysis conducted at 400 K (127 °C) showed that rotation of the amide bond was more restricted in compound **4** (containing a tertiary acetamide moiety) compared with compound **3**. At 400 K, the endo- and exo-peaks in compound **3** overlapped forming one broad singlet. However, for alkene **4**, the endo- and exo-peaks remained separated, with an endo-/exo-ratio of 1:7 at 127 °C, compared to a ratio of 1:20 obtained at room temperature. Further evidence of rotational isomerism was observed, but not investigated, in this work. For more information on the subject, we refer to relevant literature on the topic.[20−23]

3. CONCLUSIONS

Epoxide **1** was prepared over six synthetic steps with an overall yield of 25% using a strategy, where the hydroxyl groups were protected with TBS groups. Our synthesis of compound **1** enabled us to confirm the presence of epoxide **1** in the reaction mixture in small quantities during the synthesis of iodixanol

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making compound **1** a potential starting point for byproduct formation. Work is now going on in these laboratories to study whether compound **1** is involved in the byproduct formation when iodixanol is synthesized from amide **2**.

4. EXPERIMENTAL SECTION

4.1. General. All commodity chemicals and reagents were purchased from commercial suppliers and used without further purification. Petroleum ether (pet. ether, 40−65 °C) was used for column chromatography. Silica gel NORMASIL 60 40−63 μm was used for flash chromatography. Proton (^{1}H) and carbon (^{13}C) NMR spectra were acquired at 20 °C. Proton and carbon NMR spectra were recorded using an Ascend 400 NMR spectrometer from Bruker (Ascend 400), operating at 400 and 100 MHz. NMR spectra are referenced to residual dimethyl sulfoxide (DMSO) (δ 2.50 ppm, ^{1}H; δ 39.52 ppm, ^{13}C). ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), and relative integral] where multiplicity is reported as: s = singlet; d = doublet; t = triplet; q = quartet; quint = quintet; dt = doublet of triplet; m = multiplet; and bs = broad singlet. For ^{13}C NMR spectra, the data are given as chemical shift (δ), (protonicity), where the number of protons is defined as: C = quaternary (where ArC = quaternary aromatic carbon); CH = methyne; CH_2 = methylene; and CH_3 = methyl. The assignment of signals in various NMR spectra was often assisted by correlation spectroscopy (COSY), nuclear Overhauser effect and exchange spectroscopy, heteronuclear single quantum COSY, and/or heteronuclear multiple bond COSY. Analytical HPLC was performed on an Agilent 1100 or a TSP (Thermo Separation products) instrument with UV detection at 254 nm using an RP-18 column (YMC 150 × 4.6 mm, 5 μm). The following linear gradient program with mixtures of water (A) and acetonitrile (B) as eluent was applied. Program: 3.0% B (0−2.7 min), 3.0−7.2% B (2.7−5.5 min), 7.2% B (5.5−16.5 min), 7.2−13.0% B (16.5−19.5 min), 13.0−45.0% B (19.5−26.5 min), 45.0% B (26.5−31.5 min). The flow rate was 1.25 mL/min. No acid was mixed with the eluents unless otherwise stated. The amount of each component is given in percentage, based on its relative area.

*4.1.1. 5-Acetamido-N^1,N^3-bis(2,3-bis((tert-butyldimethylsilyl)oxyl)propyl)-2,4,6-triiodoisophthalamide (**3**).* Imidazole (6.58 g, 96.7 mmol), 4-dimethylaminopyridine (DMAP) (3.27 g, 26.8 mmol), and *tert*-butyldimethylsilyl chloride (13.38 g, 88.8 mmol, 6.6 equiv) were added to a solution of amide **2** (10.0 g, 13.5 mmol) in dimethylformamide (100 mL). The reaction was left stirred at 60 °C under a nitrogen atmosphere for 5 h. The reaction was then quenched with $NaHCO_3$ (sat. aq solution, 100 mL) and extracted with EtOAc (150 mL × 3), and the organic layers were washed with brine (100 mL × 2) and water (50 mL). The crude product was purified by flash column chromatography using petroleum ether/EtOAc, 7:3 → 1:4 (gradient elution). Isolation of the appropriate fractions (R_f = 0.32 in petroleum ether/EtOAc 7:3) gave 15.6 g (96%) of the O-silylated product **3** as a white solid, mp 241.0−241.5 °C. IR (KBr) ν_{max}: 3280, 2929, 2857, 2602, 2489, 2359, 1648, 1540, 1472, 1256, 1139, 1101, 984, 938, 835, 777, 668 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 and 9.52 (2br s in ratio 93:4, 1H), 8.70−8.71, 8.56−8.58, 8.32−8.37, and 8.19−8.24 (2m + 2m in ratio 78:80:18:12, 2H), 3.89−3.95 (m, 2H), 3.78−3.80, and 3.51−3.55 (2m in ratio 1:1, 4H) 3.38−3.36, 3.25−3.23, 3.15−3.13, and 3.01−2.99 (4m in ratio 1:1:1:1, 4H), 2.01 and 1.58 (2br s in ratio 27:1, 3H), 0.88, 0.87, 0.86, and 0.84 (4br s in ratio 8:6:3:1, 36H), 0.12, 0.08, 0.03, −0.05 (3br s and 1s in ratio 6:6:12:1, 24H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 169.9 (C), 168.2 (C), 150.3 (ArC), 78.6 (CH), 66.6 (CH_2), 42.8 (CH_2), 26.4 (CH_3), 23.5 (CH_3), 18.6 (C), 18.3 (C), −2.5 (CH_3), −4.0 (CH_3), −4.2 (CH_3), −4.8 (CH_3) (specific aromatic carbons were not visible because of slow relaxation and rotamerization). HRMS found: $[M + H]^+$, 1204.1972. $C_{40}H_{77}I_3N_3O_7Si_4$ requires $[M + H]^+$, 1204.1967.

*4.1.2. 5-(N-Allylacetamido)-N^1,N^3-bis(2,3-bis((tert-butyldimethylsilyl)oxy)propyl)-2,4,6-triiodoisophthalamide (**4**).* To a solution of compound **3** (15 g, 12.5 mmol) in EtOH (100 mL) and isopropyl alcohol (50 mL), a solution of H_3BO_3 (1.55 g, 25 mmol) in water (15 mL) was added with pH adjusted to approx. 12.5 by dropwise addition of 10 M KOH. Allyl bromide (1.08 mL, 12.5 mmol, 1 equiv) was added, and the reaction was left stirred for 3 h at 40 °C, whereas the pH was monitored and constantly adjusted to approx. pH 12.5 by dropwise addition of 10 M KOH. A second addition of allyl bromide (0.54 mL, 6.25 mmol, 0.5 equiv) was conducted, and the reaction was left stirred for an additional 20 h. EtOH was then removed in vacuo, the product was extracted with EtOAc (50 mL × 2), and the combined organic fractions were washed with water (40 mL). The crude product was then purified using a prepacked silica gel column (HP silica 50 μm) from PuriFlash (Interchim 215, petroleum ether/EtOAc, 95 → 50% petroleum ether (gradient elution), 35 mL/min) and yielded 13.9 g (90%) of the N-alkylated product **4** as white crystals, mp 115−116 °C. IR (KBr) ν_{max}: 3420, 3287, 3082, 2953, 2929, 2885, 2857, 2360, 2339, 2244, 1654, 1546, 1528, 1502, 1471, 1314, 1139, 1101, 982, 937, 921, 835, 778, 734, 668 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58−8.57 (m, 2H), 5.91−5.86 (m, 1H), 5.17−5.16, 5.12, 5.05, and 5.03 (4m in ratio 1:1:1:1, 2H), 4.14−4.12 and 4.06−4.04 (2m in ratio 1:1, 2H), 3.94−3.93 and 3.88−3.86 (2m in ratio 1:1, 2H), 3.78−3.75 and 3.56−3.52 (2m in ratio 1:1, 4H), 3.37−3.33, 3.26−3.24, 3.20−3.18, and 3.07−3.05 (4m in ratio 1:1:1:1, 4H), 2.1,9 2.18, 1.74 and 1.73 (4br s in ratio 1:1:20:20, 3H), 0.88, 0.87 (2br s in ratio 1:1, 36H), 0.12, 0.11, 0.08, and 0.03 (4br s in ratio 1:1:2:4, 24H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 169.3 (C), 168.5 (C), 150.8 (ArC), 146.8 (ArC), 132.6 (CH), 119.0 (CH_2), 101.1 (ArC), 100.6 (ArC), 90.8 (ArC), 71.7 (CH), 66.0 (CH_2), 50.7 (CH_2), 42.0 (CH_2), 25.9 (CH_3), 22.8 (CH_3), 18.1 (C), 17.9 (C), −4.7 (CH_3), −5.2 (CH_3); HRMS found: $[M + H]^+$, 1244.2287. $C_{43}H_{81}I_3N_3O_7Si_4$ requires $[M + H]^+$, 1244.2280.

*4.1.3. N^1,N^3-Bis(2,3-bis((tert-butyldimethylsilyl)oxy)-propyl)-5-(N-(2,3-dihydroxypropyl)acetamido)-2,4,6-triiodoisophthalamide (**5**).* To a solution of substrate **4** (12 g, 9.65 mmol) in acetone (150 mL) and water (25 mL) at room temperature were added NMO (1.8 g, 15.4 mmol, 1.6 equiv) and OsO_4 in *t*BuOH (1.95 mL, 2 mol %). The reaction was left stirred for 20 h and then quenched by the addition of $Na_2S_2O_3$ (20 mL, 1 M aq). The product was then extracted with EtOAc (50 mL × 3), and the combined organic fractions were concentrated to dryness under reduced pressure. The crude product was purified on a prepacked silica gel column (HP silica 50 μm) from PuriFlash (Interchim 215, petroleum ether/EtOAc, 95 → 40% petroleum ether (gradient elution), flow rate 35 mL/min). Isolation of the fractions with R_f = 0.19 (pet. ether/EtOAc, 11:9) gave 11.8 g (96%) of compound **5** as white crystals, mp 122−123 °C. IR (KBr) ν_{max}: 3274, 2953, 2929, 2857, 2885, 2357, 2337, 1652, 1471, 1392, 1255, 1139,

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1100, 835 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.62−8.57 (m, 2H), 4.60−4.56 (m, 2H), 3.97−3.94, 3.89−3.86 (2m in ratio 1:1, 2H), 3.91−3.88, 3.82−3.79 (2m in ratio 1:1, 1H), 3.79−3.77, 3.57−3.55 (2m in ratio 1:1, 4H), 3.38−3.42 (m, 2H), 3.83−3.81, 3.69−3.67, 3.34−3.32, 3.15−3.13 (4m in ratio 1:1:1:1, 4H), 2.24, 2.22, 1.78, and 1.77 (4br s in ratio 1:1:15:15, 3H), 0.89−0.88, 0.87−0.86 (2m in 1:1 ratio, 36H), 0.12, 0.11, 0.09, 0.04 (4br s in ratio 1:1:2:4, 24H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 170.6 (C), 169.9 (C), 151.5 (ArC), 148.6 (ArC), 100.7 (ArC), 90.9 (ArC), 72.2 (CH), 71.9 (CH), 70.4 (CH), 66.4 (CH_2), 65.0 (CH_2), 53.9 (CH_2), 42.5 (CH_2), 26.4 (CH_3), 23.3 (CH_3), 18.6 (C), 18.3 (C), −4.01 (CH_3), −4.72 (CH_3); HRMS found: $[M + H]^+$, 1278.2340. $C_{43}H_{82}I_3N_3O_9Si_4$ requires $[M + H]^+$, 1278.2335.

*4.1.4. 3-(N-(3,5-Bis((2,3-bis((tert-butyldimethylsilyl)oxy)-propyl)carbamoyl)-2,4,6-triiodophenyl)acetamido)-2-hydroxypropyl Methanesulfonate (**6**).* To a solution of diol **5** (9.5 g, 7.44 mmol) in dichloromethane (DCM) (100 mL) at 0 °C was added pyridine (5.5 mL, 68.0 mmol, 9.1 equiv), DMAP (5 mol %), and MsCl (0.92 mL, 11.9 mmol, 1.6 equiv). The reaction was left stirred for 22 h at 5 °C and was then quenched with water (50 mL), extracted with DCM (80 mL × 3), washed with HCl (75 mL, 2 M), K_2CO_3 (75 mL, sat. aq solution), and water (75 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification was conducted on a prepacked silica gel column (HP silica 50 μm) from PuriFlash (Interchim 215, petroleum ether/EtOAc, 95−30% petroleum ether (gradient elution), flow rate 35 mL/min). Excess pink/orange salt was further removed from product by filtration through silica gel (petroleum ether/EtOAc, 9:1). Isolation of the fractions with R_f = 0.19 (petroleum ether/EtOAc 1:1) gave 7.3 g (73%) of the primary mesylate **6** as white crystals, mp 146−149 °C. IR (KBr) ν_{max}: 3368, 3293, 2953, 2929, 2886, 2857, 2360, 2341, 1653, 1540, 1472, 1394, 1361, 1254, 1174, 1139, 1100, 982, 938, 835, 777 cm^{-1}; ^1H NMR (400 mHz, DMSO-d_6): δ 8.63−8.59 (m, 2H), 5.43−5.38 and 5.36−5.30 (2m in ratio 1:1, H), 4.36−4.34 and 4.12−4.10 (2m in ratio 1:1, 2H), 4.10−4.08 and 4.02−3.99 (2m, 2H), 4.02−4.00, 3.97−3.95, and 3.02−3.00 (3m, 2H), 3.96−3.94 and 3.89−3.86 (2m, H), 3.79−3.77 and 3.57−3.54 (2m in ratio 1:1, 4H), 3.42−3.41, 3.25−3.24, and 3.04−3.03 (3m, 4H), 3.17 (br s, 3H), 2.25, 2.24, 1.80, and 1.79 (4br s in ratio 2:2:13:13, 3H), 0.88 and 0.87 (2br s in ratio 1:1, 36H), 0.12, 0.09, and 0.04 (3br s in ratio 1:1:2, 24H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 170.6 (C), 169.9 (C), 73.7 (CH_2), 72.3 (CH), 71.9 (CH), 67.4 (CH), 66.4 (CH_2), 53.0 (CH_2), 42.6 (CH_2), 37.0 (CH_3), 26.4 (CH_3), 23.3 (CH_3), 22.7 (CH_3), 18.4 (C), −4.0 (CH_3), −4.1 (CH_3), −4.7 (CH_3) (aromatic carbons were not visible because of slow relaxation and rotamerization); HRMS found: $[M + Na]^+$, 1378.1935 $C_{44}H_{84}I_3N_3O_{11}SSi_4$ requires $[M + Na]^+$, 1378.1930.

Isolating of the fractions with R_f = 0.41 (petroleum ether/EtOAc 1:1) gave the dimesylated product **8** as white crystals (1.1 g, 10%), mp 152−154 °C. IR (KBr) ν_{max}: 3368, 2953, 2929, 2886, 2857, 2362, 2341, 1654, 1541, 1472, 1396, 1361, 1254, 1174, 1143, 1102, 982, 938, 834, 777 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.60−8.58, 8.52−8.50, and 8.48−8.45 (3m in 10:3:3 ratio, 2H), 4.65−4.60 and 4.45−4.43 (2m, 2H), 4.45−4.41 and 4.41−4.37 (2m, HCOMs), 4.37−4.29, 4.32−4.24, 3.44−3.36, and 3.27−3.20 (4m, 2H), 3.95−3.88 and 3.87−3.80 (2m, 2H), 3.97−3.92 and 3.91−3.86 (2m in 1:1 ratio, 4H), 3.78−3.73 and 3.30−3.19 and 3.11−2.99 (3m, 4H), 3.25 (2br s, 3H), 3.17 (br s, 3H), 2.25, 2.24, 1.80, and 1.79 (4br s in ratio 2:2:13:13, 3H), 0.88 and 0.87 (2br s in ratio 1:1, 36H), 0.12, 0.09, and 0.04 (3br s in ratio 1:1:2, 24H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 170.3 (C), 169.4 (C), 152.3 (ArC), 151.6 (ArC), 147.7 (ArC), 101.1 (ArC), 99.4 (ArC), 91.5 (ArC), 71.7 (CH), 71.4 (CH), 65.9 (CH2), 56.7 (CH_2), 52.6 (CH_2), 42.1 (CH_2), 36.9 (CH_3), 25.9 (CH_3), 25.8 (CH_3), 22.5 (CH_3), 18.1 (C), 17.9 (C), −4.5 (CH_3), −4.7 (CH_3), −5.3 (CH_3).

*4.1.5. N^1,N^3-Bis(2,3-bis((tert-butyldimethylsilyl)oxy)-propyl)-2,4,6-triiodo-5-(N-(oxiran-2-ylmethyl)acetamido)-isophthalamide (**7**).* To a solution of mesylate **6** (6.5 g, 4.8 mmol) in Et_2O (150 mL) was added NaOH (10 mL, 2 M aq). After stirring for 23 h at room temperature, the mixture was extracted with Et_2O (100 mL × 2). The extract was washed with water (75 mL) and dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 3:1). Concentration of the fractions with R_f = 0.22 (petroleum ether/EtOAc 7:3) yielded 4.2 g (70% yield) of epoxide **7** as white crystals, mp 119−120 °C. IR (KBr) ν_{max}: 3288, 3059, 2929, 2885, 2857, 2246, 1655, 1542, 1472, 1389, 1316, 1256, 1139, 1101, 981, 938, 910, 836, 778, 734, 668 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.62−8.58 (m, 2H), 3.96−3.94 and 3.90−3.88 (2m in ratio 1:1, 2H), 3.78−3.76 and 3.57−3.55 (2m in ratio 1:1, 4H), 3.70−3.69, 3.52−3.51, and 3.28−3.27 (3m, 2H), 3.41−3.39, 3.25−3.24, and 3.06−3.05 (3m, 4H), 3.28−3.26 and 3.22−3.20 (2m, 1H), 2.73−2.72, 2.51−2.49, and 2.48−2.46 (3m, 2H), 2.24, 2.23, 1.80, and 1.79 (4br s in ratio 1:1:24:24, 3H), 0.89 and 0.88 (2br s in ratio 1:1, 36H), 0.12, 0.10, and 0.05 (3br s in ratio 1:1:2, 24H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 169.3 (C), 169.2 (C), 151.0 (ArC), 147.3 (ArC), 100.4 (ArC), 91.0 (ArC), 71.7 (CH), 71.4 (CH), 65.9 (CH_2), 52.0 (CH_2), 51.3 (CH_2), 49.2 (CH), 48.7 (CH), 46.4 (CH_2), 42.0 (CH_2), 25.9 (CH_3), 24.1 (CH_3), 22.4 (CH_3), 18.1 (C), 17.9 (C), −4.5 (CH_3), −4.7 (CH_3), −5.2 (CH_3); HRMS found: $[M + H]^+$,1260.2235. $C_{43}H_{81}I_3N_3O_8Si_4$ requires $[M + H]^+$, 1260.2229.

*4.1.6. N^1,N^3-Bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(N-(oxiran-2-ylmethyl)acetamido) Isophthalamide (**1**).* To a solution of epoxide **7** (1.64 g, 1.3 mmol) in THF (35 mL) was added 1 M TBAF in THF (7.2 mL, 7.2 mmol, 5.5 equiv). After 2 h, the solvent was removed by vacuum. Three subsequent purifications using flash column chromatography EtOAc/MeOH (3:1) (R_f = 0.26) yielded 895 mg (86% yield) of epoxide **1** as a white powder, mp 285 °C (dec). IR (KBr) ν_{max}: 3343, 2926, 2350, 1730, 1650, 1429, 1393, 1347, 1316, 1270, 1173, 1110, 1044, 981, 921, 727 cm^{-1}; ^1H NMR (400 mHz, DMSO-d_6): δ 8.57 (br s, 2H), 4.77−4.75 and 4.55−4.53 (2m, 2H), 3.71−3.68 (m, 2H), 3.45−3.42 (m, 4H), 3.69−3.68, 3.57−3.56, 3.49−3.48, and 3.32−3.31 (4m, 2H), 3.49−3.48, 3.30−3.29, and 3.07−3.06 (3m, 4H), 3.26−3.24 and 3.22−3.19 (2m, 1H), 2.72−2.71, 2.52−2.51, and 2.47−2.46 (3m, 2H), 2.24, 2.22, 1.80, and 1.79 (4br s in ratio 1:1:11:11, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 169.6 (C), 169.5 (C), 151.1 (ArC), 146.6 (ArC), 100.5 (ArC), 92.1 (ArC), 70.2 (CH), 64.0 (CH_2), 51.9 (CH_2), 51.3 (CH_2), 49.3 (CH), 48.7 (CH), 46.5 (CH_2), 42.6 (CH_2), 22.5 (CH_3), 22.1 (CH_3); HRMS found: $[M + H]^+$, 803.8779. $C_{19}H_{25}I_3N_3O_8$ requires $[M]^+$, 803.8776.

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■ ASSOCIATED CONTENT

Supporting Information

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Components of the reaction mixture during preparation; HPLC chromatogram of synthesized epoxide **1** and ring-opening product iohexol; endo-/exo-configuration of compounds **3** and **4** at 298 K and 400 K; and ^{1}H, ^{13}C NMR, and/or 2D spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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