

## Supporting Information

### Enabling Amidation in Water: Micellar Catalysis Approach for Sustainable Synthesis of Iopamidol

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## 1. General remarks

Industrial grade diacyl chloride **1** and serinol were kindly provided by Bracco s.p.a. and used without further purification. All other reagents, chemical compounds and solvents were purchased from TCI Europe (Haven, Belgium), Fluorochem Europe (Hadfield, Derbyshire, United Kingdom), Alfa Aesar Europe (Kandel, Germany), Merck Life Science s.r.l. (Milano, Italy), BLD Pharmatech (Shanghai, China), abcr GmbH (Karlsruhe, Germany) and used as received without any further purification, except when otherwise stated.

The cationic Ion Exchange Resin AmberLite™ IRC-120H, Anionic Ion Exchange resin Amberstep™ 900 OH (hydroxyde form), and non-ionic adsorbent AmberLite™ XAD™ 1600 N were purchased by Acros organics, Alfa Aesar and DuPont, respectively.

Reactions are monitored by TLC (Thin Layer Chromatography) on 0.20 mm thick Polygram Sil G/UV254 silica gels, using UV light (254 nm and 365 nm), ninhydrin, KMnO<sub>4</sub> or Dragendorff stains as visualizing agents. Chromatographic purifications were performed using DAVISIL LC 60A silica gel (pore size 60 Å, 70-200 µm). Compositions of solvent mixtures used as eluents are indicated as volume/volume ratios. Melting points were determined using a Buchi M-560 (BUCHI Italia s.r.l, Cornaredo, Italy). GC-MS spectra were collected on a Clarus 560 S PerkinElmer (Perkin Elmer Italia, Milano, Italy) having an Elite-5MS 30.0 m x 250 µm column. Helium was used as carrier gas.

HPLC Agilent Technologies 1260 Infinity high resolution liquid chromatography mass spectrometry (HPLC-HRMS) system. Infinity II vial-sampler G7129A - Infinity II Multicolumn Thermostat G7116B - Infinity II Quaternary Pump G7111B - Analytical Fraction Collector G1364F - Diode Array Detector G7115A - Time of Flight (TOF) LC/MS G6230B. Column 2 ZORBAX SB-Phenyl in series, 5 µm, 4.6 x 250 mm,

NMR spectra were recorded with a Bruker NMR Avance 400 NEO instrument operating at 400 MHz (<sup>1</sup>H) and 101 MHz (<sup>13</sup>C). Resonance frequencies refer to tetramethylsilane (TMS). All chemical shifts (δ) are given in ppm and the coupling constants (J) in Hz. In the presence of oxygen-sensitive species, the water is degassed by nitrogen bubbling at the reflux temperature under vigorous magnetic agitation for at least 4 hours, taking advantage of the lower solubility of the water gases at high temperatures. Triethylamine is degassed using the freeze-pump-thaw method, which consists of vacuum freezing the species in a liquid nitrogen bath, alternating with thawing in an inert environment (under nitrogen). At least three cycles are performed. The degassed species are transferred into the reaction vessel by cannulation.

## 2. Preliminary tests

### 2.1. HPLC method

Column: 2 ZORBAX SB-Phenyl in series, 5  $\mu\text{m}$ , 4.6 x 250 mm,

Flux: 1 mL/min

Detector: UV 240 nm

Temperature: 20 °C

Solvent A: water

Solvent B: water/acetonitrile 1:1 v/v

Time (min)	%A	%B
0	100	0
18	100	0
40	62	38
45	50	50
50	100	0
60	100	0

### 2.2. Synthesis of N<sup>1</sup>,N<sup>3</sup>-dihexyl-5-(2-hydroxypropanamido)-2,4,6-triiodoisophthalamide

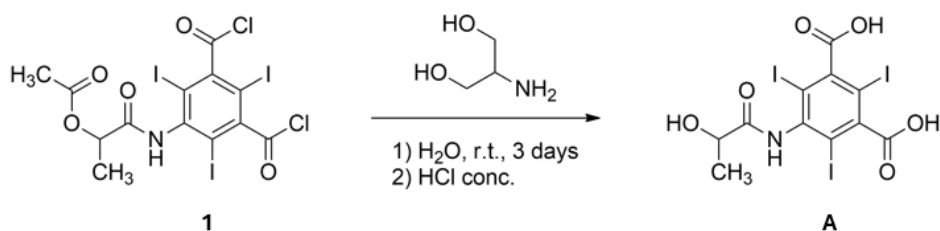


Acyl chloride **1** (7.10 g, 0.0100 mol) is dispersed in 20 ml of TX-100 10 wt% aqueous solution, when the mixture is homogeneous n-hexylamine is added dropwise (6.6 mL, 5.06 g, 0.0500 mol). The reaction mixture is stirred for 30 min at room temperature and monitored via TLC. The product is recovered by filtration, washed with 25 mL of deionized water and dried in vacuum oven at 45 °C. A white solid is obtained (7.2 g, 88%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K) –  $\delta$  5.23 (q, J= 6.9 Hz, 1H), 3.16 (m, 4H), 2.12 (d, J=3.8 Hz, 3H), 1.53 (m, 7H), 1.34 (m, 4H), 1.25 (m, 8H), 0.86 (t, J= 6.8 Hz, 3H). <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>, 298 K)  $\delta$  169.39 [C], 169.11 [C], 167.90 [C], 150.26 [C], 142.16 [C], 98.61 [C], 90.26 [C], 69.36 [CH], 38.89 [CH<sub>2</sub>], 31.32 [CH<sub>2</sub>], 29.07 [CH<sub>2</sub>], 26.67 [CH<sub>2</sub>], 22.11 [CH<sub>2</sub>], 20.81 [CH<sub>3</sub>], 17.55 [CH<sub>3</sub>], 13.94 [CH<sub>3</sub>].

### 3. Preliminary screening of surfactants

Even though serinol is highly water soluble and we did not expect that its direct reaction with chloride **1** in water could provide a viable method for the synthesis of iopamidol, we carried out a series of test reactions to identify the most suitable surfactant for our scope as well as to test the reactivity of **1** under standard micellar amidation conditions involving lipophilic amines.

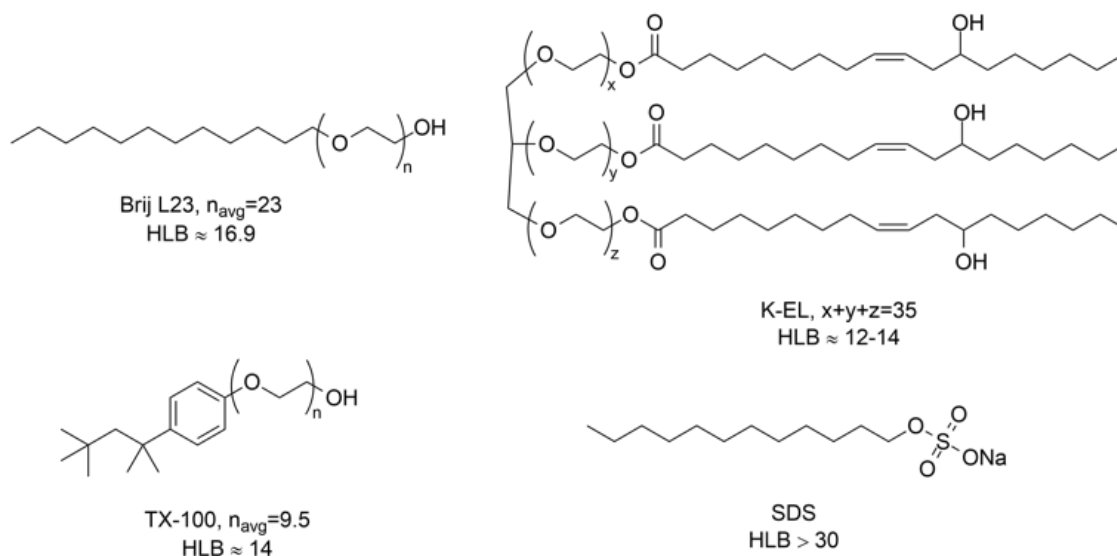
The selection of the appropriate surfactant for a micellar reaction involves consideration of several factors such as compatibility with reactants and solvents, solubility, required HLB value, ionic or non-ionic nature, temperature and pH conditions, environmental and safety considerations, cost effectiveness and the performance in similar reactions. We favoured the use of well-known industrial surfactants due to their wide market availability and lower cost. Before investigating the behaviour of the different surfactants, the amidation reaction was tested in water alone (“on-water conditions”)<sup>1,2</sup>, since many reactions can be carried out in water medium, even with undissolved reactants.



Scheme S1. Amidation of chloride **1** with serinol, carried out under on-water conditions.

Working at a formal concentration of 0.5 M of **1** and a 5:1 molar ratio between serinol and **1**, at room temperature, in water alone as the reaction medium, only the quantitative formation of the hydrolysed and deacetylated product **A** is observed, which is isolated by filtration after acidification of the reaction mixture with HCl 37 wt% (Scheme S1). This outcome was expected and aligns with previous research, affirming the necessity of a surfactant to inhibit the competing hydrolysis reaction of the acyl chloride, particularly under alkaline conditions. We thus turned to the use of surfactants, selecting three neutral (Kolliphor EL, Triton X-100, Brij L23) and one anionic (Sodium Dodecyl Sulphate, SDS) derivatives.

Kolliphor EL (K-EL) (0.32 €/g, from Aldrich catalogue) is a surfactant some of us are familiar with for micellar catalysis and features a Hydrophilic Lipophilic Balance (HLB) in the 12-14 range, making it a hydrophilic emulsifier with a relatively low polarity, suitable for the formation of oil in water emulsion. This is in accordance with the use of water as the dispersing phase and of the reagents as the disperses, emulsified one. Triton X-100 (TX-100) (0.07 €/g, from Aldrich catalogue) features a very similar HLB of 14, it is used as detergent and wetting agent and features the presence of a benzene ring in the lipophilic portion that could be profitably exploited to interact with the aromatic portion of compound **1**. Brij L23 (0.14 €/g, from Aldrich catalogue) is a higher polarity surfactant, traditionally used as solubilizer for cosmetics, pharmaceuticals, and household products.<sup>3</sup> It does not feature aromatic and unsaturated functionalities and thus complements the characteristics of both K-EL and TX-100. Finally, Sodium Dodecyl Sulphate (SDS) (0.04 €/g, from Aldrich catalogue), in an anionic, hydrophilic, and very polar surfactant, frequently used for emulsion polymerization reactions. Scheme S2 shows the molecular structure of the surfactants employed in this study.



Scheme S2. Chemical structure of the industrial surfactants considered for the amidation of **1** with serinol.

Table 1 of the main text summarizes the results we obtained. None of the conditions we tested can be considered a viable method to produce iopamidol, yet we gained relevant insights on the potentialities and limits of the direct amidation method. All reactions were carried out at ambient temperature and under standard laboratory environment.

Entries 1-4 show that while working at 4 wt% surfactant concentration, results only marginally improve with respect to the on-water reaction. Complete hydrolysis and deacetylation of **1** dominate the product distribution and only in the case of TX-100, a little iopamidol formation is observed. As we already mentioned, the poor solubility of **1** limits the kinetics of all reactions, to the point that complete conversion requires 3 days. Increasing the surfactants concentration to 10 wt% positively impacted on both the dispersibility of the chloride (see Figure 1 in the main text) and the overall reaction outcome (Entry 5). Pushing the approach to the limit, we increased TX-100 concentration up to 50 wt%, finally observing sizeable formation of iopamidol (63%) alongside with the monoamidation product (35%) and negligible hydrolysis (1%). Yet, working at such high surfactant concentration hardly represents a micellar catalysed reaction anymore and removal and recycle of the surfactant becomes a very serious issue.

1 R. N. Butler and A. G. Coyne, *Organic and Biomolecular Chemistry*, 2016, **14**, 9945–9960.

2 S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angewandte Chemie - International Edition*, 2005, **44**, 3275–3279.

3 M. Ash and I. Ash, *Handbook of industrial surfactants*, Synapse Information Resources, Inc, Endicott, NY, 5th editio., 2010, vol. 1.

## 4. Micellar amidation

### 4.1. General Protocol

A 10 wt% solution is prepared by dispersing TX-100 in water, the closed reaction vessel is immersed in a cold water bath (approximately 18-20 °C). Diacyl chloride **1** (0.5 M, 1 eq) is added and dispersed under magnetic stirring for 2 h. The lipophilic derivative (2 eq) is added as a solution (or dispersion) in Et<sub>3</sub>N (3 eq), the addition takes 30 min-1 h. After 2-24 h the reaction is stopped and the crude product recovered by filtration on Büchner funnel (except product of amidation with derivative **13**, see Section 3.2). Reactions were performed on a small scale using approximately 1-2 g of **1**.

### 4.2. Protocol variations

By employing milled diacyl chloride **1** (15 min, 15 Hz, ZrO<sub>2</sub> jars), instead of the commercial one, it is possible to sensibly decrease the concentration of TX-100 from 10 wt% to 2 wt%, enabling shorter reaction times (avoiding the dispersion phase), a more homogeneous reaction mixture and facile product recovery.

In some experiments, DIPEA (2.2 eq) was used instead of Et<sub>3</sub>N as a base, in order to investigate the formulation behavior with a more lipophilic base.

Amidation product of lactofaluro with derivative **13** is an oil. The product was isolated by centrifugation, followed by extraction with CH<sub>2</sub>Cl<sub>2</sub>, washing with water, and solvent evaporation under reduced pressure.

### 4.3. One-pot procedure for preparation of iopamidol (Table 2, tests K1 and K2)

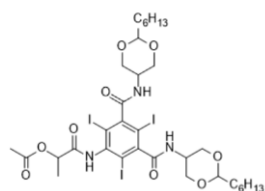
A 2 wt% solution is prepared by dispersing TX-100 in water, the closed reaction vessel is immersed in a cold water bath (approximately 18-20 °C). Milled diacyl chloride **1** (0.5 M, 1 eq) is added and dispersed under magnetic stirring for 5 minutes before the addition of the lipophilic derivative (**11** or **13**, 2 eq) as a solution in Et<sub>3</sub>N (3 eq). The addition takes 30 min. After 3 h, a 0.5 M solution of HCl is added, and the reaction is stirred at room temperature for the appropriate time, after which an oil separate. The reaction mixture is extracted with AcOEt, and the organic phase discarded. The aqueous phase is purified over cationic and anionic exchange resins, followed by elution over XAD 1600 resin (water is used as the eluent). Iopamidol is recovered after water evaporation.

Test K1: reaction performed on 1.42 g of lactofaluro and 1.11 g of derivative **11**. After addition of aqueous HCl (20 mL), reaction mixture is stirred overnight before extraction with 10 mL of AcOEt. After purification, 0.90 g of iopamidol were recovered (1.16 mmol, 58% yield)

Test K2: reaction performed on 1.23 g of lactofaluro and 1.50 g of derivative **13**. After addition of aqueous HCl (11 mL), reaction mixture is stirred for 30 minutes, and extracted with 10 mL of AcOEt. After purification, 0.93 g of iopamidol were recovered (1.20 mmol, 69% yield)

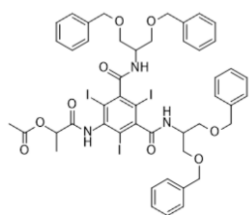
#### 4.4. $^1\text{H}$ - and $^{13}\text{C}$ - NMR product characterization

Recording the  $^{13}\text{C}$ -NMR spectra of molecules characterized by an iopamidol-based core is particularly problematic. Despite working with very concentrated samples due to the low abundance of  $^{13}\text{C}$  the sensitivity of  $^{13}\text{C}$ -NMR is intrinsically much lower than that of  $^1\text{H}$ -NMR. Quaternary carbons often have longer  $T1$  values. This is because the main source of dipole-dipole relaxation, the protons, are not directly bound to them. Protons near the carbon nucleus usually help accelerate relaxation, and their lack slows down this process, resulting in longer  $T1$  times. Aromatic carbons and alkyne carbons tend to have longer  $T1$  compared to alkyl carbons. This is because the  $\pi$ -electrons delocalize and affect the efficiency of relaxation. If  $T1$  is long, the carbon nuclei take longer to return to equilibrium after excitation. Therefore, signals from these carbons may be weak or absent from the spectrum. Also the proximity of a bonded heavy atom (such as iodine) can contribute in depressing  $^{13}\text{C}$ -NMR signals due to an increase in the broadness caused by spin-orbit coupling. Iodine, in particular, due to its high polarizability contributes to fluctuations in the local magnetic field, increasing the relaxation rate  $T2$  and further contributing in line broadening. Our targets are characterized by a tri-iodine aromatic core made up entirely of quaternary carbons, in some cases the nearest proton is more than 5 bonds away, decisively too far away to allow effective relaxation. As a result, it is rarely possible to image all quaternary carbons of that species, despite the fact that high scan numbers ( $n_s > 12000$ ) have been employed.



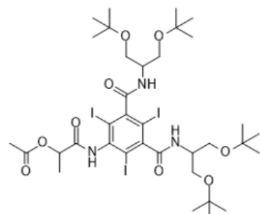
*Bis-amidation product with serinol derivative 5*

$^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  9.64 (br, 1H), 8.85 (br, 1H), 6.91-6.87 (m, 1H), 5.39-5.34 (m, 1H), 4.54 (m, 1H), 4.21-4.06 (m, 6H), 3.94-3.89 (m, 4H), 2.21 (s, 3H), 1.64-1.52 (m, 7H), 1.35-1.24 (m, 16H), 0.85 (t,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}$ -NMR (101 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  170.04, 169.64, 168.96, 168.83, 149.16, 142.78, 103.24, 99.17, 89.26, 70.53, 69.50, 69.27, 44.43, 34.83, 29.78, 29.10, 23.91, 22.64, 21.34, 17.99, 14.16.



*Bis-amidation product with serinol derivative 8*

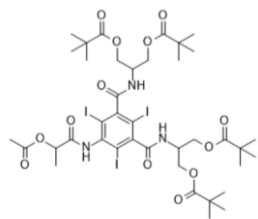
$^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  9.53 (br, 1H), 8.59 (br, 1H), 7.31-7.26 (m, 20H), 6.30 (br, 1H), 6.23-6.20 (m, 1H), 5.42 (q,  $J = 6.8$  Hz, 1H), 4.53-4.50 (m, 8H), 4.42 (br, 2H), 3.81-3.60 (m, 8H), 2.24-2.21 (m, 1H), 1.64 (d,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$ -NMR (101 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  170.08, 169.58, 169.10, 168.92, 149.44, 142.71, 137.97, 128.55, 127.94, 127.88, 98.98, 89.02, 73.42, 70.57, 67.74, 67.50, 49.31, 21.43, 17.99.



*Bis-amidation product with serinol derivative 9*

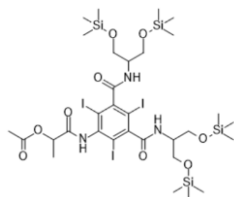
$^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  9.90 (br, 1H), 8.77 (br, 1H), 6.37-6.20 (m, 2H), 5.42 (q,  $J = 6.7$  Hz, 1H), 4.26 (m, 2H), 3.62-3.58 (m, 4H), 3.45-3.42 (m, 4H), 2.28 (s, 3H), 1.64 (d,  $J = 6.8$  Hz, 3H), 1.17-1.16 (m, 36H).  $^{13}\text{C}$ -NMR (101 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  170.24, 169.81, 168.97, 168.84, 149.69, 142.74, 99.11, 98.96, 89.32, 73.26, 73.23, 73.15, 73.11, 70.62, 58.82, 58.76, 58.66, 49.89, 27.75, 21.56, 18.08.





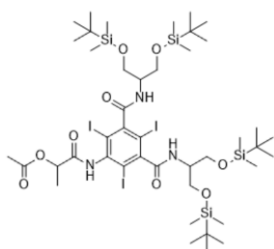
*Bis-amidation product with serinol derivative 10*

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  5.47 (q,  $J = 6.9$  Hz, 1H), 4.29 – 4.18 (m, 2H), 3.69 – 3.59 (m, 8H), 2.24 (s, 3H), 1.64 (d,  $J = 6.9$  Hz, 3H), 1.21 (d,  $J = 6.2$  Hz, 36H).  $^{13}\text{C-NMR}$  (101 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  178.26, 169.52, 149.29, 88.59, 83.27, 70.58, 61.67, 38.90, 27.25, 21.15, 17.62.



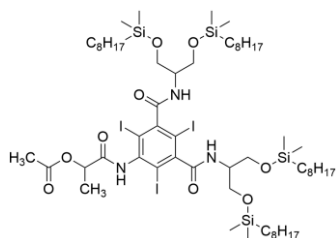
*Bis-amidation product with serinol derivative 11*

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  9.69 (br, 1H), 8.52 (br, 1H), 6.26-6.12 (m, 2H), 5.42 (q,  $J = 6.8$  Hz, 1H), 4.15 (m, 2H), 3.88-3.84 (m, 4H), 3.65-3.60 (m, 4H), 2.27 (s, 3H), 1.64 (d,  $J = 6.8$  Hz, 3H), 0.13-0.11 (m, 36H).  $^{13}\text{C-NMR}$  (101 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  169.93, 169.55, 168.88, 168.74, 98.88, 98.76, 89.06, 70.50, 59.07, 58.88, 51.78, 21.34, 17.88, -0.50.



*Bis-amidation product with serinol derivative 12*

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  9.77 (br, 1H), 8.54 (br, 1H), 6.30-6.09 (m, 2H), 5.40 (q,  $J = 6.8$  Hz, 1H), 4.14 – 4.07 (m, 2H), 3.93 – 3.86 (m, 4H), 3.71 – 3.64 (m, 4H), 2.25 (s, 3H), 1.64 (d,  $J = 6.8$  Hz, 3H), 0.89-0.87 (m, 36H), 0.07 – 0.05 (m, 24H).  $^{13}\text{C-NMR}$  (101 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  170.10, 169.68, 169.16, 169.00, 149.63, 142.86, 99.21, 98.96, 88.89, 70.62, 59.91, 59.53, 52.48, 26.12, 26.08, 21.47, 18.49, 18.41, 18.02, -5.15.



*Bis-amidation product with serinol derivative 13*

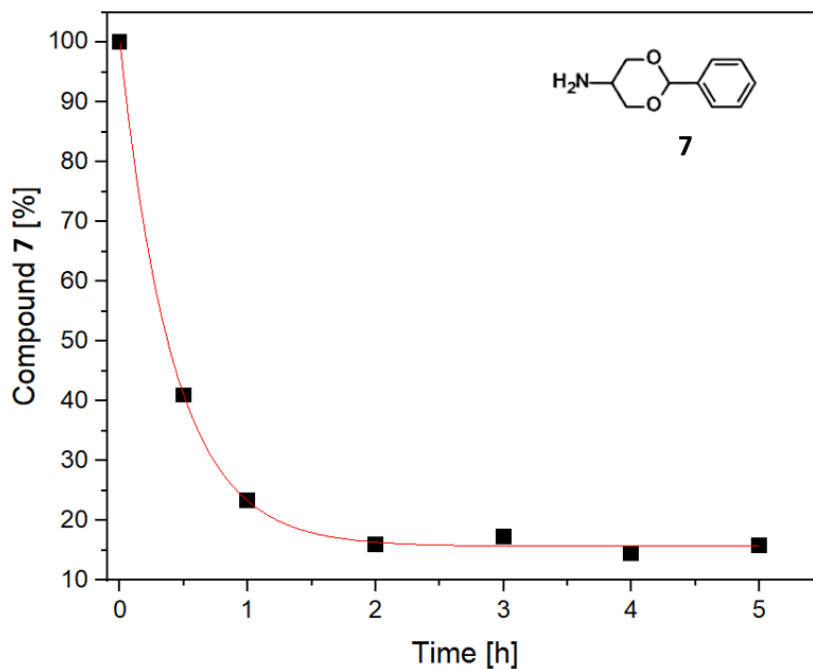
$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  9.69 (br, 1H), 8.30 (br, 1H), 6.29-6.13 (m, 2H), 5.42 (q,  $J = 6.5$  Hz, 1H), 4.12 (m, 2H), 3.88 – 3.84 (m, 4H), 3.63 – 3.57 (m, 4H), 2.26 (s, 3H), 1.64 (d,  $J = 6.8$  Hz, 3H), 1.31-1.26 (m, 48H), 0.89-0.86 (m, 12H), 0.60-0.57 (m, 8H), 0.11 (s, 24H). Attempts to record the  $^{13}\text{C-NMR}$  of this derivative were unfruitful, as cleavage of the dimethyloctylsilyl chains is observed during the experiment, leading to precipitation of the deprotected product.

#### 4.5. Stability test acetals & ketals by GC-MS internal standard method

*Experimental protocol:* [R-NH<sub>2</sub>] concentration in water as reaction protocol, Et<sub>3</sub>N 3 eq, TX-100 2 wt%, Room temperature, internal standard tetrahydronaphthalene (THN)

The lipophilic serinol derivative, triethylamine and THN are introduced in a TX-100 2 wt% aqueous solution, vigorously stirred. At fixed times, a 0.1 mL aliquot is taken from the stirred mixture and diluted with 1 mL of deionized water. The solution is saturated with NaCl and extracted with 2 mL of AcOEt. The organic phase is dried on anhydrous Na<sub>2</sub>SO<sub>4</sub> and then filtered on a silica pad. The solution is transferred in an GC-MS vial and analyzed.

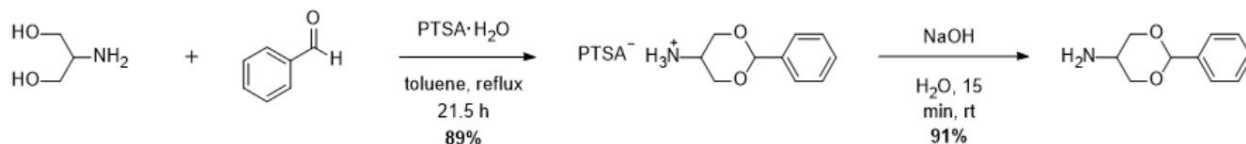
*GC-MS method:* 100 °C – 3 min, 20 °C/min up to 320 °C



For the acetals **5** and **7** the inhomogeneity of the mixtures did not allow reproducible sampling, so it was not possible to observe the decomposition trend. For derivative **6** no signal from the pristine molecule or its decomposition products is observed in GC-MS, as the species and its hydrolysis products preferentially partition into water and not in the AcOEt used for extraction. In the case of derivative **4**, the trend confirms the hypothesis of a significant hydrolysis in the timeframe in which the reaction occurs. The concentration of derivative **4** under the reaction conditions halved within 30 minutes from the start of the experiment.

## 5. Synthesis of lipophilic serinol derivatives

### 5.1. 2-Phenyl-1,3-dioxan-5-amine (derivative 4)

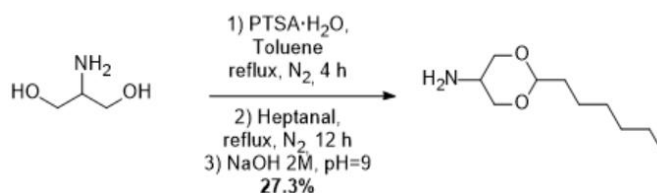


*Step A* - Serinol (15.229 g, 0.167 mol) and PTSA·H<sub>2</sub>O (35.580 g, 0.184 mol) are dispersed in toluene (240 mL), under magnetic stirring. The mixture is refluxed for 1 h and the crystallization water of PTSA is distilled by Dean-Stark apparatus. Benzaldehyde (17.25 mL, 0.167 mol) is added dropwise. The mixture is refluxed for 21.5 h. When the reaction mixture is cooled to rt, a white solid precipitates. The p-toluene sulphonate serinol is recovered by filtration on Buchner and washed with 2-PrOH (50 mL). (52.3 g, mp 193-199 °C, 89.0%). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.51 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.42 (dd, *J* = 5.0, 1.7 Hz, 3H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.73 (s, 1H), 4.29 (ddd, *J* = 63.8, 13.2, 1.3 Hz, 4H), 3.47 (s, 1H), 2.33 (s, 3H).

*Step B* - Intermediate A is dispersed in 0.31 M NaOH (500 mL) and stirred for 15 min. The solution is saturated with NaCl and extracted with AcOEt (4x150 mL). The organic phase is dried on Na<sub>2</sub>SO<sub>4</sub> and concentrated by rotavapor to obtain a yellow oil (24.21 g, 91%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K) δ 7.42 – 7.36 (m, *J* = 6.5, 2.9 Hz, 2H), 7.35 – 7.30 (m, 3H), 5.53 (s, 1H), 3.98 (dd, *J* = 104.1, 11.2 Hz, 4H), 2.73 (s, 1H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 138.26, 128.96, 128.28, 125.93, 101.78, 73.30, 45.79.

### 5.2. 2-Hexyl-1,3-dioxan-5-amine (derivative 5)



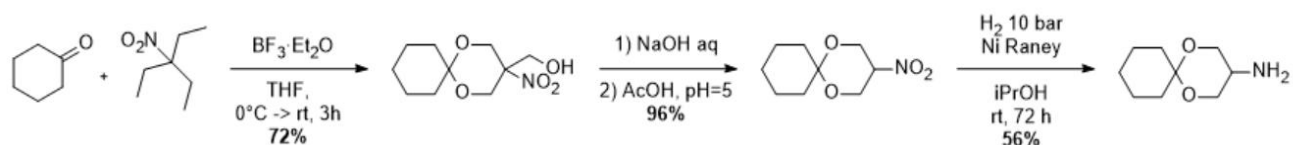
Serinol (2.50 g, 27.44 mmol) and 98% PTSA·H<sub>2</sub>O (5.74 g, 30.18 mmol) are introduced in a two necked round bottom flask equipped with a Dean-Stark apparatus, and the system is put under nitrogen atmosphere. Toluene (78 mL + 15 mL for filling the Dean-Stark) is injected from a septum located on the top of the Allihn condenser. The PTSA crystallization water is removed by azeotropic distillation. Heptanal (2.82 g, 24.70 mmol) is added dropwise and the reaction mixture is refluxed for 12 h removing the water by azeotropic distillation. The mixture is cooled to rt and a white solid precipitates. From <sup>1</sup>H NMR analysis the solid is a mixture of serinol PTSA and the desired product. The solid is dissolved in water (50 mL), 2 M NaOH is added to the solution up to pH=9 and saturated

with NaCl. The aqueous phase is extracted with diethyl ether (3 x 50 mL), the organic phase dried on Na<sub>2</sub>SO<sub>4</sub> then concentrated by evaporation under reduced pressure. A yellow oil is obtained (1.2633 g, 27.3%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K) δ 4.46 (t, J = 5.1 Hz, 1H), 3.87-3.79 (m, 4H), 2.64 (m, 1H), 2.25 (br, 2H), 1.58-1.52 (m, 2H), 1.34-1.19 (m, 8H), 0.81 (t, J = 6.9 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, 298 K) δ 102.75 [CH], 72.60 [CH<sub>2</sub>], 45.76 [CH], 34.93 [CH<sub>2</sub>], 31.65 [CH<sub>2</sub>], 29.05 [CH<sub>2</sub>], 23.69 [CH<sub>2</sub>], 22.46 [CH<sub>2</sub>], 13.96 [CH<sub>3</sub>].

### 5.3. 2,2-dimethyl-1,3-dioxan-5-amine (derivative 6)

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### 5.4. 1,5-dioxaspiro[5.5]undecan-3-amine (derivative 7)

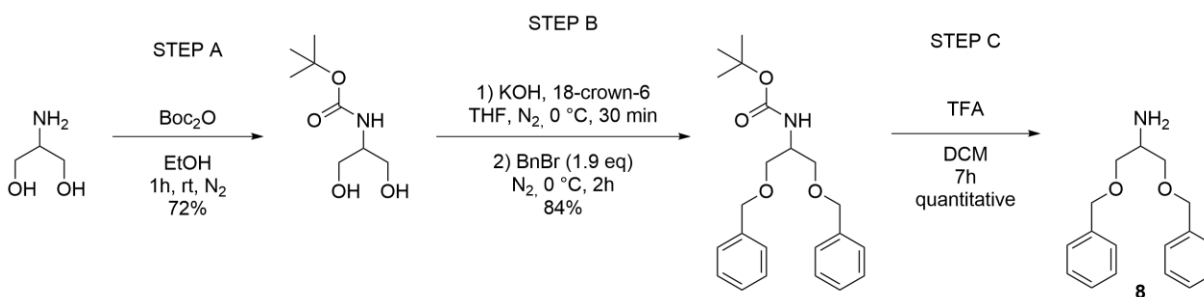


*Step A- (3-nitro-1,5-dioxaspiro[5.5]undecan-3-yl)methanol:* 2-Methyl-2-nitropropane-1,3-diol (14.00 g, 0.09263 mol) is dissolved in 150 mL of THF by magnetic stirring. Cyclohexanone (10.00 g, 0.10189 mol) is added at room temperature. Boron trifluoride diethyl etherate is added dropwise in an ice bath and then kept stirring at room temperature for 3 hours. Product formation is checked by TLC (SiO<sub>2</sub>, DCM/MeOH 9:1): the product is detected by potassium permanganate. Saturated NaHCO<sub>3</sub> solution is added to the reaction mixture, then the mixture is extracted three times with ethyl acetate, dried on anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated. Purification by batch chromatography was performed. 6 g of the product is adsorbed on 120 g of silica in a flask, and washed with the petroleum ether /ethyl acetate mixture starting from 9:1 in gradient up to 7:3. After evaporation, the product is crystallized by petroleum ether and filtered under vacuum and dried. The overall yield is 72% (15.36 g, 0.066 mol). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 298 K) δ 5.47 (t, J=5.7, 1H), 4.35 (d, J=13.0 Hz, 2H), 4.07 (d, J=13.0 Hz, 2H), 3.73 (d, J=5.8 Hz, 2H), 1.83 (m, 1H), 1.51-1.35 (m, 8H); <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>, 298 K) δ 98.3 [C], 87.7 [C], 62.4 [CH<sub>2</sub>], 60.4 [CH<sub>2</sub>], 35.3 [CH<sub>2</sub>], 28.4 [CH<sub>2</sub>], 24.9 [CH<sub>2</sub>], 22.1 [CH<sub>2</sub>], 22.0 [CH<sub>2</sub>].

*Step B- 3-nitro-1,5-dioxaspiro[5.5]undecane:* Sodium hydroxide (3.70 g, 0.09297 mol) is dissolved in 20 mL of deionized water. The white crystalline solid product (4.30 g, 0.01859 mol) is added and gradually dissolved at room temperature. After one hour, the reaction is cooled to 10.0 °C, and acetic acid is added dropwise to obtain a solution pH=5, in which a white precipitate is formed. The precipitate (3.60 g, 0.01798 mol, 96% yield) was then filtered under vacuum, and washed with petroleum ether. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 298 K) δ 4.62 (m, 1H), 4.38 (bd, J=13.3 Hz, 2H), 4.29 (bd, J=13.0 Hz, 2H), 1.87 (m, 2H), 1.45-1.36 (m, 8H); <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>, 298 K) δ 98.2 [C], 77.9 [CH], 58.7 [CH<sub>2</sub>], 36.7 [CH<sub>2</sub>], 27.4 [CH<sub>2</sub>], 25.0 [CH<sub>2</sub>], 22.1 [CH<sub>2</sub>], 22.0 [CH<sub>2</sub>].

*Step C- 1,5-dioxaspiro[5.5]undecan-3-amine:* The white solid compound (2.40 g, 0.012 mol) is dissolved in 10 mL of isopropanol. A 50% Raney-Nickel (4 g, 0.014 mol) is washed with isopropanol and centrifuged three times to completely remove water, then added to the reaction mixture. The reaction is stirred at room temperature under hydrogen atmosphere (10 bar) for 72 hours, then filtered through Celite and dried under vacuum. Product formation is checked by TLC (SiO<sub>2</sub>, Toluene/isopropanol 8:2) and detected by Dragendorff reagent. The product is purified by column chromatography (toluene/isopropanol from 9:1 in gradient up to 7:3) and dried under vacuum to give the amine as a yellowish oil (1.14 g, 0.0067 mol, 56% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K) δ 3.98 (dd, J=11.6, 3.2, 2H), 3.52 (dd, J=11.7, 5.5, 2H), 2.80 (m, 1H), 1.85 (bs, 2H), 1.72 (m, 4H), 1.59 (m, 4H), 1.38 (m, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, 298 K) δ 97.9 [C], 65.4 [CH<sub>2</sub>], 45.2 [CH], 33.3 [CH<sub>2</sub>], 31.4 [CH<sub>2</sub>], 25.5 [CH<sub>2</sub>], 22.4 [CH<sub>2</sub>], 22.3 [CH<sub>2</sub>].

### 5.5. 1,3-Bis(benzyloxy)propan-2-amine (derivative 8)



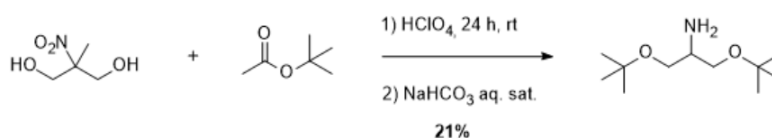
*Step A: tert-butyl (1,3-dihydroxypropan-2-yl)carbamate* - Serinol (23.81 g, 0.261 mol) is dissolved in EtOH (200 mL) (dried on 3 Å activated carbide molecular sieves), by magnetic stirring in a round bottom flask, at room temperature and under nitrogen. In a second round bottom flask, di-tert-butyl dicarbonate (74.09 g, 0.339 mol) is dissolved in dry EtOH (100 mL) under nitrogen. The Boc<sub>2</sub>O solution is cannulated in the former reaction flask in 30 min. A cooling bath is arranged at the bottom of the first round bottom flask, due to the exothermicity of the reaction. The reaction is monitored by GC-MS. After 1.5 h the reaction is completed. The solvent is removed by evaporation under reduced pressure and a white solid is obtained. The solid is dissolved in deionized water (70 mL) and then extracted with AcOEt (2 x 200 mL), the organic phase is dried on anhydrous sodium sulfate and concentrated by rotavapor. The raw product is crystallized from heptane (24 mL) and washed on the filter with cold heptane (14 mL). The purified product is a white needle-like solid (36 g, 72%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K) δ 3.77 (ddd, J = 27.4, 11.1, 4.5 Hz, 4H), 3.69 – 3.61 (m, 1H), 1.44 (s, 9H).

*Step B: tert-butyl (1,3-bis(benzyloxy)propan-2-yl)carbamate* - Tert-butyl (1,3-dihydroxypropan-2-yl)carbamate (28.488 g, 0.149 mol), 85% KOH (59.01 g, 0.894 mol) and 18-crown-6 (1.575 g, 5.96 10<sup>-3</sup> mol) are dissolved in THF (500 mL), under nitrogen. Benzyl bromide is added dropwise in 30 min. The reaction is performed in an ice and water bath and monitored via TLC with ninhydrin stain (Eluent: heptane, AcOEt 7:3). The reaction is

completed in 2 h. The reaction mixture is filtered on celite and washed with 200 mL of Et<sub>2</sub>O. The obtained solution is concentrated by evaporation under reduced pressure. The waxy solid is dispersed in 70 mL of ETP and decanted at 60 °C until the separation of the phases, the upper layer is recovered and cooled at -10 °C by an ice and water bath, the white solid precipitated is recovered by filtration on Büchner funnel (yield 84%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K) δ 7.39 – 7.28 (m, 10H), 4.96 (Bd, *J* = 6.4 Hz, 1H), 4.52 (s, 4H), 3.99 (m, 1H), 3.64 (dd, *J* = 9.2, 4.2 Hz, 2H), 3.56 (dd, *J* = 9.2, 6.0 Hz, 2H), 1.45 (s, 9H).

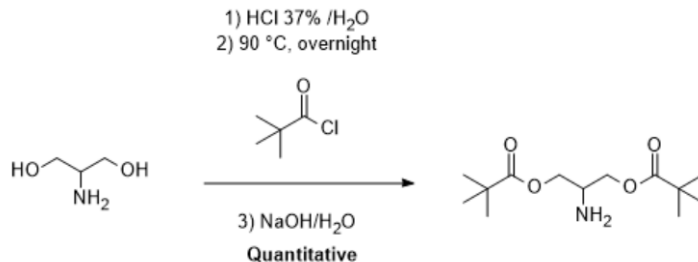
*Step C: 1,3-bis(benzyloxy)propan-2-amine* - Tert-butyl (1,3-bis(benzyloxy)propan-2-yl)carbamate (3.263 g, 8.785 mmol) is dispersed in DCM (59 mL), under magnetic stirring. Trifluoro acetic acid (6.010 g, 52.71 mmol) is added dropwise at rt. After 7 h the reaction is completed. The reaction mixture is concentrated by rotavapor and dispersed in water (10 mL). 2 M NaOH is added until pH=9 is reached. The aqueous phase, saturated with NaCl, is extracted with AcOEt (3 x 70 mL), dried on anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated by evaporation under reduced pressure. A yellow oil is obtained (2.04 g, quantitative). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K) δ 7.32 – 7.21 (m, 10H), 4.46 (s, *J* = 6.2 Hz, 4H), 3.58 – 3.51 (dd, 4H), 3.47 – 3.40 (m, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, 298 K) δ 138.4 (Ar), 128.5 (Ar), 127.8 (Ar), 73.4 (OCH<sub>2</sub>Ar), 72.8 (CHCH<sub>2</sub>O), 51.2 (NHCH).

## 5.6. 1,3-di-tert-butoxypropan-2-amine (derivative 9)



2-Methyl-2-nitropropane-1,3-diol (3.00 g, 0.0329 mol) is suspended in 45 mL of tert-butyl acetate by magnetic stirring. 3.63 mL (0.0600 mol) was added dropwise. The reaction mixture was left under magnetic stirring for 24 hour at room temperature. Reaction was slowly quenched in to 25 mL of saturated aqueous solution of sodium bicarbonate. Organic layer was separated, and aqueous layer was extracted twice with ethyl acetate. Combined organic layer was washed with water, dried over sodium sulphate and the solvent was removed by vacuum distillation. Purification by column chromatography was performed (toluene/methanol 9:1). The product was dried under vacuum to give the amine as a brownish oil (1.30 g, 0.006 mmol, 21% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K) δ 3.38 (dd, *J*=8.6, 4.7, 2H), 3.24 (dd, *J*= 8.5, 6.6, 2H), 2.99 (m, 1H), 1.90 (bs, 2H), 1.18 (s, 18H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, 298 K) δ 72.6 [C], 64.0 [CH<sub>2</sub>], 51.8 [CH], 27.5 [CH<sub>3</sub>].

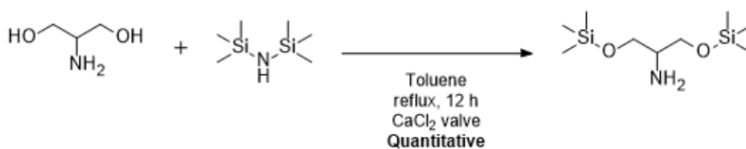
### 5.7. 2-Aminopropane-1,3-diyl bis(pivalate) (derivative 10)



Serinol (1.080 g, 11.85 mmol) is dispersed in water (3 mL) in a 25 mL reaction flask. 37% aq. HCl is added to the solution up to pH=1. The mixture is dried by rotavapor and then dried in vacuum at 40 °C for 3 h, a white solid is obtained. After the addition of pivaloyl chloride (2.97 mL, 2.930 g, 24.30 mmol), the reaction mixture is heated at 90 °C, from GC-MS the reaction is completed overnight. The residual pivaloyl chloride is removed by distillation in vacuum. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 298 K) δ 1.15 (18H, s) 3.55–3.78 (1H, m), 4.06–4.37 (4H, m), 8.77 (3H, bs). <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>, 298 K) δ 26.88 [CH<sub>3</sub>], 48.06 [C], 58.66 [CH], 61.05 [CH<sub>2</sub>], 177.26 [C].

The crude product is dissolved in deionized water (15 mL) and 2 M NaOH is added up to pH=9, the mixture is stirred for 1 h and then extracted with AcOEt (3x10 mL). The organic phase is dried on anhydrous Na<sub>2</sub>SO<sub>4</sub> and then the solvent removed by rotavapor. A white waxy solid is obtained (3.07 g, quantitative). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K) δ 4.05 (qd, *J* = 11.0, 5.6 Hz, 4H), 3.30 (m, 1H), 1.21 (m, 18H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 178.04 [C], 65.69 [CH<sub>2</sub>], 49.31 [CH], 39.47[C], 27.10 [CH<sub>3</sub>].

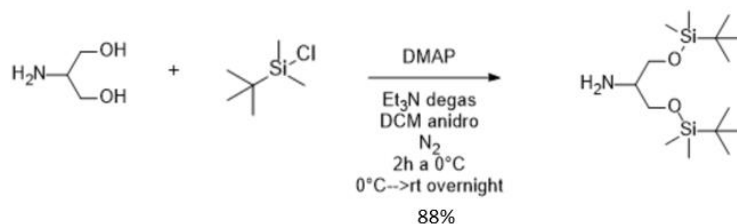
### 5.8. 2,2,8,8-tetramethyl-3,7-dioxa-2,8-disilanonan-5-amine (derivative 11)



Serinol (4.56 g, 50.00 mmol) is dissolved in toluene (40 mL) in a 100 mL two necked round bottom flask. Water traces are removed by azeotropic distillation by Dean-Stark apparatus. The solution is cooled at room temperature and Dean-Stark apparatus is removed. The system is equipped with an Allihn condenser and CaCl<sub>2</sub> valve, Hexamethyldisilane (HMDS) (12.2 g, 75.49 mmol) is added and the reaction mixture refluxed for 12 h. The reaction is monitored via GC-MS. The solvent and the residual HDMS are removed by distillation in vacuum. The product is a colorless oil (**Quantitative**).

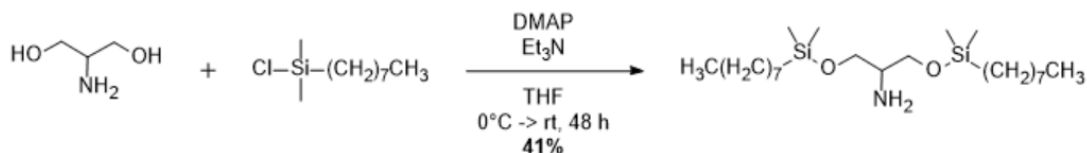
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K) δ 3.63 – 3.34 (m, 4H), 3.02 – 2.81 (m, 1H), 0.10 (s, 18H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, 298 K) δ 64.50 [CH<sub>2</sub>], 54.20 [CH], -0.49 [CH<sub>3</sub>].

### 5.9. 1,3-Di-tert-butyltrimethylsilyloxy-2-propylamine (derivative 12)



The glassware employed is firstly dried overnight in an oven at 110 °C. Degassed Et<sub>3</sub>N is prepared via freeze pump thaw method. Serinol (2.000 g, 21.95 mmol) and DMAP (0.0122 g, 0.0997 mmol) are introduced in a 250 mL two necked flask, after 3 cycles of vacuum/nitrogen the system is placed under nitrogen atmosphere. The powders are dispersed in anhydrous DCM (40 mL). After setting a cooling ice bath, the degassed Et<sub>3</sub>N is added (8.685 g, 85.83 mmol). The mixture is stirred for 1 h. In a second roundbottom flask, a solution of TBDMS-Cl (6.452 g, 42.81 mmol) in anhydrous DCM (33 mL) is prepared under nitrogen atmosphere. Such TBDMS-Cl solution is added dropwise in the former reaction flask and the reaction is stirred for 2 h at 0 °C then at rt overnight. The following day the reaction is quenched with deionized water (40 mL), the organic phase is washed with of deionized water (3x10 mL). The organic phase is stirred with 85% KOH (5.000 g) for 20 min, the solid is then filtered, and the organic phase washed again with water (2x5 mL), dried on anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated by evaporation under reduced pressure. A light yellow oil is obtained with a 88% of mass recovery. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 298 K) δ 3.58 (dd, *J* = 9.8, 5.2 Hz, 2H), 3.49 (dd, *J* = 9.8, 5.7 Hz, 2H), 2.84 (p, *J* = 5.5 Hz, 1H), 0.88 – 0.87 (m, 18H), 0.05 – 0.01 (m, 12H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, 298 K) δ -3.4 [CH<sub>3</sub>Si], 18.4 [CH<sub>3</sub>], 26.0 [C], 54.5[CH], 64.9[CH<sub>2</sub>O].

### 5.10. 9,9,15,15-tetramethyl-10,14-dioxa-9,15-disilatricosan-12-amine (derivative 13)



2-Aminopropane-1,3-diol (4.00 g, 0.0439 mol) is dissolved in THF (20 mL) by magnetic stirring. Triethylamine (15.6 g, 0.154 mol) is added dropwise at room temperature, followed by 4-dimethylaminopyridine. The reaction mixture is cooled in an ice bath and chlorodimethyl(octyl)silane (22.7 g, 0.110 mol) is added dropwise. The ice bath is removed, and the mixture stirred at room temperature for 48 hours. The reaction is monitored by TLC (SiO<sub>2</sub>, eluant: ethyl acetate/petroleum ether 8:2, developed by dipping in the Dragendorff reagent. The reaction mixture is evaporated under vacuum and the dark oily residue is purified by a first column chromatography (eluent: dichloromethane/methanol 9:1) followed by a second one (ethyl acetate/petroleum ether 9:1- 7:3). The product



was dried under vacuum to give the amine as a yellowish oil (7.80 g, 0.0181mol, 41% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  3.58 (dd,  $J = 9.9, 5.1$  Hz, 2H), 3.46 (dd,  $J = 9.9, 6.0$  Hz, 2H), 2.88 (q,  $J = 5.5$  Hz, 1H), 1.75 (bs, 2H), 1.29 (m, 24H), 0.89 (t,  $J = 6.8$  Hz, 6H), 0.59 (m, 4H), 0.09 (s, 12H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ , 298 K)  $\delta$  64.5 [ $\text{CH}_2$ ], 54.2 [ $\text{CH}$ ], 33.5 [ $\text{CH}_2$ ], 31.9 [ $\text{CH}_2$ ], 29.33 [ $\text{CH}_2$ ], 29.27 [ $\text{CH}_2$ ], 23.2 [ $\text{CH}_2$ ], 22.7 [ $\text{CH}_2$ ], 16.3 [ $\text{CH}_2$ ], 14.1 [ $\text{CH}_3$ ], -2.2 [ $\text{SiCH}_3$ ].

## 6. Green metrics

E-factor, the amount of organic waste produced per unit amount of product, was calculated as

$$E_f = \frac{\text{mass of waste}}{\text{mass of product}} = \frac{\text{mass of organic reagents} + \text{mass of solvents} - \text{mass of product}}{\text{mass of product}}$$

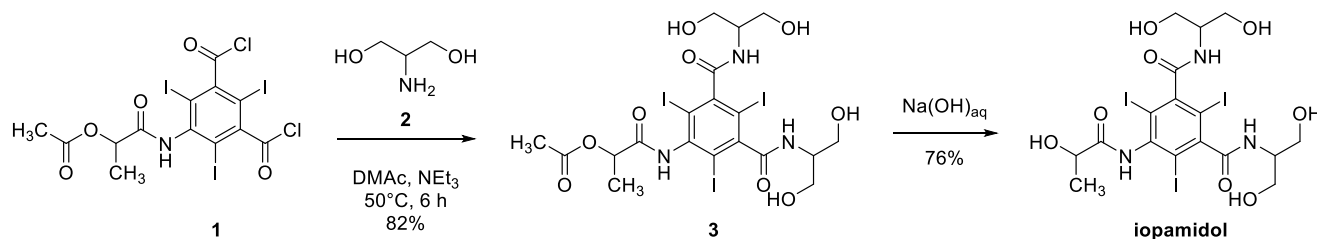
If several steps are needed to synthesize the product, for every synthetic step the required amounts of reagents and solvents required to obtain 1 gram of the final product are calculated.

E-factor of the literature process was calculated on the basis of the data reported in patent WO2012175903A1.

E-factor of the process described in this paper was calculated on the basis of the amount of organics used for the synthesis of derivative **11** and iopamidol according to the one-pot procedure (see main text, Table 2, test K1 and section 3.3 of ESI).

In both cases, purification with cationic, anionic and XAD 1600 resins was not considered as water only is needed. We did not take water needed for purification into account because the volumes required for such a filtration are so large that any other difference in the reaction is completely outshined by the sheer amount of water. However, this water is completely recovered by distillation and recycled, therefore we feel comfortable with our decision of not including it in the reaction metrics to better highlight the difference between our method and the literature approach.

## 6.1. Literature procedure

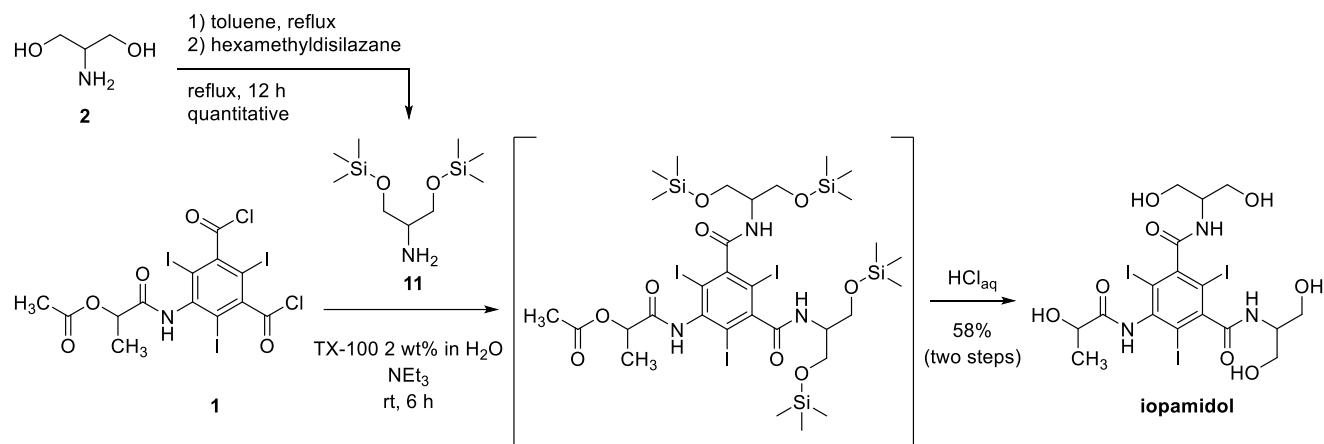


Chemical	Amount used	Amount needed for 1 g of product
<b>Step 1 – synthesis of acetyl-iopamidol (3)</b>		
Lactofaluro (1)	20 g	1.46 g
Serinol (2)	6.4 g	0.47 g
NEt <sub>3</sub>	7.26 g (10 mL)	0.53 g
DMAc	93.7 g (100 mL)	6.83 g
<b>Purification of acetyl-iopamidol (3)</b>		
Ethanol	15.8 g (20 mL)	1.15 g
Acetone	94.2 g (120 mL)	6.86 g
Acetyl-iopamidol (3)	<b>19 g</b>	<b>1.38 g</b>
<b>Step 2 – synthesis of iopamidol</b>		
Acetyl-iopamidol (3)	18 g	1.38 g
<b>Purification of iopamidol</b>		
Ethanol	80.5 g (102 mL)	6.19 g
Iopamidol	<b>13 g</b>	<b>1.00 g</b>

The E-factor of the process therefore is

$$E_f = 1.46 + 0.47 + 0.53 + 6.83 + 1.15 + 6.86 + 6.19 - 1.00 = 22.5$$

## 6.2. Procedure described in this work



Chemical	Amount used	Amount needed for 1 g of product
<b>Step 1 – synthesis of protected serinol (derivative 11)</b>		
Serinol (2)	4.56 g	0.476 g
Hexamethyldisilaxane	12.2 g	1.27 g
Toluene	35.5 g (40 mL)	3.71 g
Derivative 11	<b>11.77 g</b>	<b>1.23 g</b>
<b>Step 2 – one-pot synthesis of iopamidol</b>		
Lactofaluro (1)	1.42 g	1.58 g
Derivative 11	1.11 g	1.23 g
Et <sub>3</sub> N	0.601 g	0.668 g
Triton X-100	0.100 g	0.111 g
<b>Purification of iopamidol</b>		
Ethyl acetate	0.902 g (10 mL)	1.00 g
Iopamidol	<b>0.90 g</b>	<b>1.00 g</b>

The E-factor of the process therefore is

$$E_f = 0.476 + 1.27 + 3.71 + 1.58 + 0.668 + 0.111 + 1.00 - 1.00 = 7.82$$