

# Highly Selective Synthesis of 2-(2*H*-1,2,3-Triazol-2-yl)benzoic Acids

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## Supporting Information

**ABSTRACT:** A selective and scalable synthesis of 2-(2*H*-1,2,3-triazol-2-yl)benzoic acid starting from 1-fluoro-2-nitrobenzene derivatives is presented. The four-step synthesis introduces the triazole at the start via *N*<sup>2</sup>-arylation of 4,5-dibromo-2*H*-1,2,3-triazole. A sequence of consecutive functional group transformations, namely hydrogenation, Sandmeyer iodination, and Grignard carboxylation, provides the target molecules in a reliable and scalable manner. The usefulness of this method is demonstrated by the synthesis of di- or tri(2*H*-1,2,3-triazol-2-yl)benzene derivatives, which are difficult to produce by other methods.

**KEYWORDS:** orexin, 2*H*-1,2,3-triazoles, Sandmeyer reaction, Grignard reaction, scale-up

## INTRODUCTION

Dual orexin antagonists (DORA), like suvorexant, are used to treat primary insomnia. A patent screen in 2016 by Roch and Boss showed that many patents were filed in the field of DORA demonstrating the high interest in this topic.<sup>1</sup> Many Active Pharmaceutical Ingredients (APIs) described in this screen have a common structural element: a 2-(2*H*-1,2,3-triazol-2-yl)benzamide (Figure 1). Therefore, an efficient and general synthesis of triazole benzoic acids is of high interest. A one step synthesis to prepare these compounds via copper catalyzed arylation of 1,2,3-triazole with 2-iodo- or 2-bromobenzoic acids was described by Buchwald et al.<sup>2</sup> A mixture of *N*-1 and *N*-2 isomers is formed, which had to be separated by crystallization or by column chromatography. This approach was employed successfully for the synthesis of Suvorexant by Merck.<sup>3</sup> The regioisomers of the benzoic acid were separated via crystallization of the corresponding sodium benzoate. A highly *N*<sup>2</sup>-selective palladium catalyzed arylation of 1,2,3-triazoles was introduced by Buchwald et al.<sup>4</sup> Yields of 46–91% and excellent *N*<sup>2</sup>-selectivity of >95% were obtained. Since the triazole is a good directing group, these derivatives could straightforwardly be converted to benzoic acids via C–H activation. Palladium catalyzed halogenation,<sup>5</sup> ethoxycarbonylation,<sup>6</sup> and rhodium catalyzed cyanation were the key steps in these transformations.<sup>7</sup> Barth et al. produced the benzoic acid of Suvorexant by deprotonating 2-(*p*-tolyl)-2*H*-1,2,3-triazole with *tert*-butyllithium at –80 °C and trapping the anion with CO<sub>2</sub>.<sup>8</sup> The precursor was produced via copper catalyzed cyclization of glyoxal tolylosazone.<sup>9</sup>

For the Idorsia Orexin program, different triazole benzoic acids 5a–8a on gram to kilogram scale were on demand (Figure 2). A selective, general approach was chosen for their synthesis. These procedures should further scale-up to 10 kg. The strategy described by Wang et al., who found that 4,5-dibromo-1,2,3-triazole was arylated highly selectively at the *N*-2 position, seemed attractive to us:<sup>10</sup> 2-fluoronitrobenzenes reacted with dibromotriazole in >90% yield to single regioisomers, and further reduction by hydrogenation afforded the *ortho* triazole anilines. Our intention was to convert the anilines into iodobenzenes via a Sandmeyer reaction.

Halogen–magnesium exchange and trapping of the Grignard species with CO<sub>2</sub> should afford the desired products. These procedures should be safe, robust, and suitable for a further scale-up to 10 kg.

## RESULTS AND DISCUSSION

**Synthesis of 2-(2*H*-1,2,3-Triazol-2-yl)benzoic Acids 5a–d.** The synthesis started with the 1-fluoro-2-nitrobenzene derivatives 6a–d, which are available on kilogram scale, and with dibromo triazole, which was prepared in high yield from triazole, bromine, and sodium hydroxide in water (Scheme 1).<sup>11</sup> The *N*-arylation was performed with potassium carbonate as base in DMF at elevated temperatures according to the literature procedure.<sup>10</sup> The products 7a–d were precipitated by addition of water and isolated by filtration. The yields were high (78–95%), and purity by LC-MS was greater than 98% area percent (% a/a). The *N* – 1 isomers could not be observed. The hydrogenation of the nitro compounds 7a–d was performed in a 3 L double jacketed autoclave. EtOAc was chosen as solvent and Pd/C as catalyst. The reduction of the nitro group was fast at the beginning, but the reaction stalled due to catalyst poisoning by the generated HBr. In the presence of triethylamine, the nitro reduction was sluggish. If potassium or sodium acetate (2.1 equiv) was present from the beginning, the nitro reduction and debromination proceeded smoothly. The hydrogenation was exothermic and conversion was complete after 1–2 h to cleanly produce the desired anilines. The exothermicity of the reaction could easily be controlled by adjusting the stirrer speed. Filtration of the catalyst, aqueous work up, and precipitation of the anilines as sulfates salts from isopropanol afforded the desired products 8a–d in high yields and purities. The sulfate salts were chosen since the subsequent Sandmeyer reaction was run in aqueous sulfuric acid. At first, the aryl bromide was targeted. Diazotization was performed with *tert*-butyl nitrite in acetonitrile in the presence of CuBr<sub>2</sub><sup>12</sup> or in water with

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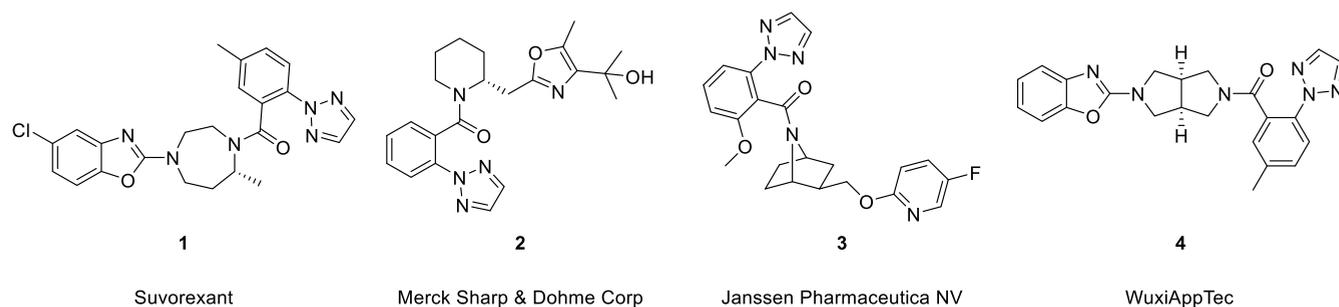


Figure 1. Selection of DORA APIs (2–4) from a patent screen of 2016 and Suvorexant 1.

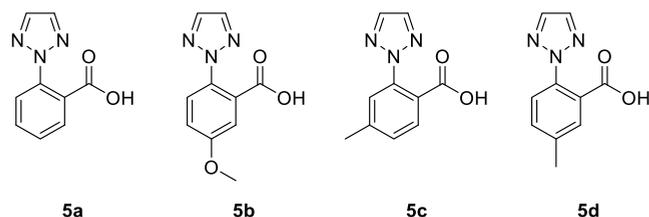


Figure 2. 2-(2H-1,2,3-Triazol-2-yl)benzoic acid 5a–d.

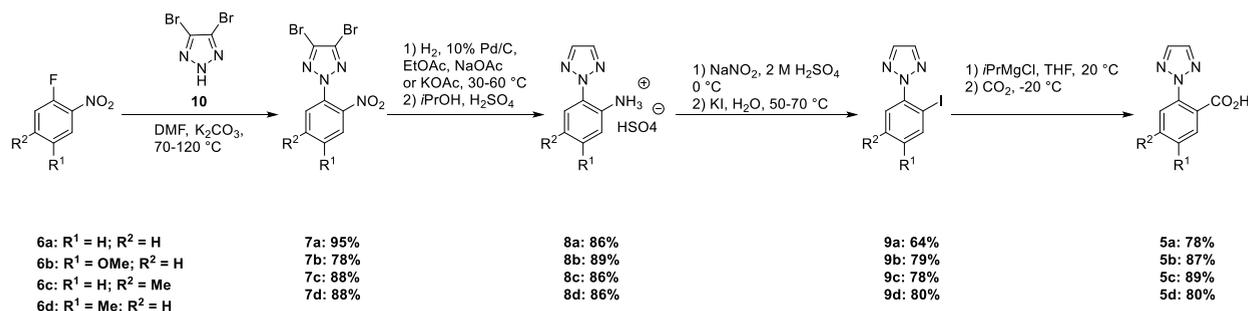
sodium nitrite in the presence of CuBr. In general, the reaction provided the products in 60–95% yield after purification, but the work ups were challenging due to insoluble copper salts. Therefore, we focused on the synthesis of the iodides **9a–d** as they are accessible without Cu salts. Instead, water-soluble potassium iodide as halogen source was used. Sulfate **8a** was dissolved in aqueous sulfuric acid and treated with 1 equiv of sodium nitrite at 0–5 °C. The diazonium salt was stable over a period of 24 h at room temperature, as judged by LC-MS. In addition, no gas evolution could be observed over this period. Therefore, the diazonium salt solution was deemed stable at 0–5 °C and safe for a scale-up to 10 kg. For a further scale-up, more safety investigation should be carried out. A solution of potassium iodide in water was heated to 60–70 °C, and the diazonium salt solution was added carefully in a dosed controlled fashion. The conversion of the diazonium salt to the product **9a** directly after addition was >95%, as judged by LC-MS. After aging at 60–70 °C for 20 min the reaction provided the product in a purity of ca. 80% a/a. As a minor impurity, 2-phenyl-2H-1,2,3-triazole was present with 2% a/a. This impurity was easily removed in the next step. Two impurities with 9 respectively 6% a/a with a mass of 415 g/mol [M + 1] were problematic, because they were also converted into carboxylic acids in the subsequent step. We were not able to purify acid **5a** by crystallization. Fortunately, distillation of the iodophenyl triazole at  $4 \times 10^{-3}$  mbar and 84 °C head

temperature provided the product **9a** in high purity 97% a/a as a yellow oil. The iodide **9a** was still contaminated by the 2-phenyl-2H-1,2,3-triazole. In the final step, **9a** was reacted with *i*PrMgCl in THF at –20 °C. An aliquot was treated with ammonium chloride and analyzed by LC-MS, proving a complete I/Mg-exchange. CO<sub>2</sub> was bubbled through the reaction mixture at –20 to –10 °C. The addition was exothermic, and the color changed from brown to yellow. The exothermicity of the reaction was controlled by the feeding rate of the CO<sub>2</sub>. After the exotherm had ceased, the mixture was treated with aqueous HCl. THF was removed by distillation, and the product was extracted into DCM. The crude product was crystallized from toluene, and **5a** was obtained in a yield of 78% as a yellow solid with a purity of >99% a/a. The overall yield of the four-step sequence was 41%, and 22 g of the benzoic acid **5a** was produced.

For **5b**, the procedure was similar to that for **5a**, except the Sandmeyer reaction produced the iodide **9b** in a much cleaner fashion. The reduced product was not observed and the purity of the crude product was >98% a/a. In addition, the purity of the product could be further upgraded by recrystallization from *i*PrOH. Benzoic acid **5b** was produced on 1 kg scale in an overall yield of 48%. The procedure was further scaled up at a custom manufacturer to 10 kg without issues.

The synthesis of benzoic acid **5c** held similar challenges as the synthesis of **5a**. The iodination of **8c** delivered an oily product which was not clean enough for the following step. Again, a purification by distillation was necessary. In total ca. 3 kg of crude material was produced which was distilled on a short path distillation apparatus with a recovery of 2.5 kg. The jacket temperature was adjusted to 120 °C and the vacuum to 0.004 mbar. The yield of the Sandmeyer reaction was 78%. The benzoic acid **5c** was produced once more on 1 kg scale and on 10 kg with an external partner without issues. The isomer **5d** was made on 100 g scale. Interestingly, the Sandmeyer product **9d** was isolated as an orange solid in

### Scheme 1. Synthesis of Triazole Benzoic Acids 5a–d from 1-Fluoro-2-nitrobenzenes 6a–d





60 °C on 50 g scale. After the consumption of ca. 50% of the theoretical amount of hydrogen, a thick suspension formed. We speculated that some intermediate aniline prior debromination precipitated. The reaction was completed after 3 h, and a nicely stirrable suspension was formed. The reaction mixture was filtered at room temperature, and product **13** was isolated after crystallization from *i*PrOH in a yield of 80%.

The 2,6-substituted nitrobenzene **17** was reduced with similar reaction conditions, but once more a thick suspension formed after the consumption of 33% of hydrogen. Again at the end of the reaction the suspension was better stirrable. The usual work up afforded **18** in a yield of 86%. Based on these observations the reduction of the triple substituted nitro compound **22** should be challenging with regard to the low solubility of the aniline intermediate. Hence, the external temperature was increased to 70 °C, the amount of EtOAc increased from 10 to 20 volumes, and 60% more catalyst was used. In practice, more than 500 g of nitrobenzene **22** was reduced in 5 batches.<sup>14</sup> The reaction mixtures (thick suspensions) were combined and filtered. The usual work up afforded the product in a yield of ca. 5%: it turned out that aniline **23** precipitated in EtOAc and was filtered off with the catalyst. The filter cake was rinsed with copious amounts of THF, acetonitrile, and DCM. Finally, 52 g of **23** was isolated in a yield of 30%. The aniline **23** was suspended in *i*PrOH (10 vol) and treated with sulfuric acid (1.05 equiv). The sulfate salt was not formed, instead **23** was recovered from this mixture with 98% by filtration. The reduction of the nitro compound **22** was repeated on 50 g scale. This time the mixture was filtered over paper, the filtrate was discarded, and the cake was suspended in 6 vol of TFA. The suspension was filtered over Celite, the filtrate was concentrated, and the residue was taken up in *i*PrOH. Aniline **23** was isolated with an improved yield of 69%.

The Sandmeyer reaction was checked on 5 g scale with the sulfate salt of **13**. The salt did not dissolve in 10 vol of aqueous sulfuric acid and upon addition of sodium nitrite the diazonium salt formed but precipitated. The suspension was added to an aqueous solution of potassium iodide at elevated temperatures and the product **14** was formed in 81% yield. The reaction was scaled up to 60 g and delivered **14** with a reduced yield of 57%. Some sulfate salt of **13** was not converted due to the low solubility in the reaction mixture. Despite these issues, 40 g of iodide **14** was produced. For the synthesis of 2,6-substituted iodide **19** the same problems occurred. The yield of **19** was only 19% on 14 g scale. Since the sulfate salt of tritriazole substituted aniline **23** was impossible to form, the Sandmeyer reaction seemed challenging. Indeed, the reaction in sulfuric acid with sodium nitrite showed no conversion to the diazonium salt by LC-MS. Finally, 2 M HCl (10 vol) and acetonitrile (20 vol) were tried. As expected the starting material did not dissolve, but upon addition of sodium nitrite a clear solution was formed. The iodide **24** was formed in 86% yield. Two more runs on 10 and 31.5 g went smoothly with reproducible yields of 85 and 81%, respectively. The products were combined and recrystallized from *i*PrOH, and a total of 46 g of **24** was produced. With this improved procedure in hand, the Sandmeyer reaction with the 2,4-ditriazole aniline **13** and the 2,6-ditriazole aniline **18** was repeated. The yield was 81% for iodide **14** and 91% for **19**, but most importantly no issues with precipitated diazonium salts were encountered.

With the iodides **14**, **19**, and **24** available, the iodine–magnesium exchange followed by quench with electrophiles could be investigated. The 2,4-bis-triazole iodide **14** converted cleanly to the corresponding benzoic acid **15a** (97% yield) and the benzaldehyde **15b** (91% yield). While 2,6-substituted benzoic acid **20a** was produced in 87% yield, the benzaldehyde **20b** was only formed in 36% yield. When DMF was added to the Grignard species, ca. 20% of 1,3-di(2*H*-1,2,3-triazol-2-yl)benzene was formed. Two crystallizations from *i*PrOH and acetone were necessary to purify **20b**. The tris-triazole derivative **24** reacted with *i*PrMgCl in THF, but the Grignard species precipitated. Nevertheless, the formation of benzoic acid **25a** was accomplished in a yield of 97%. The production of the benzaldehyde **25b** was troubled by the formation of ca. 30% of the reduced product **25c**. **25c** was even less soluble than **25b**, and purification via crystallization was difficult. **25b** could be isolated in a yield of 10% and a purity of 98% from the mother liquor. **25c** was produced on purpose by simple addition of saturated ammonium chloride solution to the reactive Grignard intermediate. Aqueous HCl was added to the reaction mixture, and the product was collected by filtration in excellent yield. The off-white product showed a melting point of 398 °C (DSC). Analysis of the highly symmetrical compound was difficult due to solubility issues. The product was not sufficiently soluble in DCM, THF, EtOAc, acetone, DMF, or DMSO even at elevated temperatures. Strong acids were identified as good solvents. The product was well soluble in sulfuric acid, TFA, or trifluoromethanesulfonic acid. Unfortunately, reasonable NMR spectra in D<sub>2</sub>SO<sub>4</sub> or in deuterio TFA could not be obtained. In the end, it was possible to dissolve **25c** in deuterio TFA and dilute the mixture with CDCl<sub>3</sub>. This sample preparation was successful and <sup>1</sup>H and <sup>13</sup>C spectra were obtained. A LC-MS chromatogram was recorded and a purity of 98.8% a/a was determined and a mass of 280 g/mol [M + 1] was detected.

## CONCLUSION

Four *ortho* (2*H*-1,2,3-triazol-2-yl)benzoic acids **5a–d** have been synthesized in four steps to support our in-house orexin program. The aim was to prepare the different compounds with a general method, which should be suitable to produce gram and several kilogram quantities in a reliable and safe manner. Several methods are described in the literature (*vide supra*) to install the triazole moiety, and we opted for the selective and high yielding procedure via 4,5-dibromo-2*H*-1,2,3-triazole from Wang et al.<sup>10</sup> Hence, the anilines **8a–d** were straightforwardly produced and further derivatized to the iodides and finally to the benzoic acids in excellent yields and purities. The general method was employed for the synthesis of compounds bearing two or three triazole moieties (**15**, **20**, and **25**). In addition, the highly symmetric 1,3,5-tri(2*H*-1,2,3-triazol-2-yl)benzene **25c** was produced on gram scale.

## EXPERIMENTAL SECTION<sup>15</sup>

**General.** Compounds are characterized by <sup>1</sup>H NMR (500 MHz, Bruker) or <sup>13</sup>C NMR (125 MHz, Bruker). Details for the LC–MS methods are listed in the [Supporting Information](#). The purity is given in area percent (% a/a). Unless stated otherwise, yields are given as is without correcting for purity.

**4,5-Dibromo-2*H*-1,2,3-triazole (10).** 1*H*-1,2,3-Triazole (1347 g, 19.5 mol) and water (6.7 L) were charged to a 30 L glass lined reactor. The solution was heated to 45 °C. To the

solution was added bromine (1 L, 19.5 mol) at 45–48 °C over a period of 20 min (exothermic addition). After five minutes a white suspension was formed. To the suspension was dosed simultaneously 50% aqueous NaOH solution (2027 mL, 38 mol) and bromine (1 L, 19.5 mol) at 40–52 °C over a period of 30 min (very exothermic addition). The suspension was cooled to 20 °C and treated with 40% aqueous bisulfite solution (350 mL). The suspension was filtered, and the cake was washed with water (6 L). The product was dried on a 20 L rotavap at 60 °C under reduced pressure for one hour to yield an off white solid. Yield: 4.23 kg (96%). Purity (LC-MS method 2): 100% (210 nm),  $t_R$  0.66 min, mp 192 °C (DSC (onset), decomposition);  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_6$ -DMSO)  $\delta$ : 124.2.

**4,5-Dibromo-2-(2-nitrophenyl)-2H-1,2,3-triazole (7a).** A mixture of fluoro-2-nitrobenzene **6a** (100 g, 0.709 mol),  $\text{K}_2\text{CO}_3$  (97.9 g, 0.709 mol), DMF (450 mL), and 4,5-dibromo-2H-1,2,3-triazole **10** (161 g, 0.709 mol) was stirred at 80 °C overnight. The suspension was diluted with  $\text{H}_2\text{O}$  (1.5 L) at 50 °C and filtered at 22 °C. The cake was rinsed with  $\text{H}_2\text{O}$  (500 mL) and *i*PrOH (500 mL). The product was dried under reduced pressure at 50 °C to yield an off-white solid. Yield: 234 g (95%). Purity (LC-MS method 2): 100% (210 nm),  $t_R$  1.00 min, mp 124 °C (DSC);  $^1\text{H}$  NMR (500 MHz,  $\text{D}_6$ -DMSO)  $\delta$ : 8.18 (d,  $J = 8.1$  Hz, 1H), 8.02 (m, 1H), 7.96 (m, 1H), 7.84 (m, 1H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_6$ -DMSO)  $\delta$ : 143.3, 134.9, 131.8, 131.2, 128.7, 126.6, 126.0.

**2-(2H-1,2,3-Triazol-2-yl)aniline Sulfate (8a).** Nitro compound **7a** (213 g, 0.612 mol), KOAc (127 g, 1.29 mol) and 10% Pd/C (50% wet, 32.6 g), EtOAc (1 L), and  $\text{H}_2\text{O}$  (100 mL) were charged to a 3 L double jacketed autoclave equipped with a hollow shaft stirrer, equipped with a hydrogen pressflow. The reaction mixture was pressurized 3 times to 3 bar with nitrogen and two times with hydrogen to 3 bar. The suspension was stirred under hydrogen (1 bar) for 2 h at 65 °C. The reaction mixture was cooled to 22 °C and filtered over paper. Layers were separated, and the organic layer was washed with 16% aqueous NaOH (320 mL) and  $\text{H}_2\text{O}$  (2  $\times$  250 mL). The organic layer was concentrated to dryness under reduced pressure. The residue was diluted with *i*PrOH (1 L) and heated to 60 °C. Concentrated  $\text{H}_2\text{SO}_4$  (60 g, 0.612 mol) was added. The suspension was cooled to 20 °C and filtered. The product was dried under reduced pressure at 60 °C to yield a white solid. Yield: 135.8 g (86%). Purity (LC-MS method 2): 100% (210 nm),  $t_R$  0.68 min;  $[\text{M} + 1]^+ = 161$ , mp 195 °C (DSC);  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ )  $\delta$ : 7.96 (m, 2H), 7.89 (d,  $J = 8.0$  Hz, 1H), 7.49 (m, 2H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_2\text{O}$ )  $\delta$ : 136.8, 132.5, 130.1, 129.6, 125.2, 123.6, 122.2.

**2-(2-Iodophenyl)-2H-1,2,3-triazole (9a).** Aniline **8a** (10 g, 0.039 mol) was dissolved in 2 M  $\text{H}_2\text{SO}_4$  (50 mL), and the solution was cooled to 0 °C. A solution of sodium nitrite (2.67 g, 0.039 mol) in  $\text{H}_2\text{O}$  (15 mL) was added, keeping the internal temperature below 10 °C. The solution was stirred for 10 min. In another flask, potassium iodide (9.64 g, 0.058 mol) was dissolved in  $\text{H}_2\text{O}$  (15 mL) and the solution was heated up to 70 °C. The diazonium salt solution was added over 10 min. The dark foaming mixture was stirred for two hours at 70 °C. The mixture was cooled to 22 °C. Isopropyl acetate (100 mL) was added, and the layers were separated. The organic layer was washed with  $\text{H}_2\text{O}$  (100 mL), sat. aqueous thiosulfate solution (100 mL), and  $\text{H}_2\text{O}$  (100 mL). The organic layer was concentrated under reduced pressure to give a brown oil as crude material (9.8 g). The product was purified by distillation

at  $3 \times 10^{-3}$  mbar (head temperature: 85–95 °C) to afford a yellow oil as product. Yield: 6.7 g (64%). Purity (LC-MS method 2): 97% (210 nm),  $t_R$  0.86 min;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.99 (m, 1H), 7.89 (m, 2H), 7.47 (m, 2H), 7.18 (m, 1H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.2, 140.4, 135.6, 130.9, 128.9, 127.8, 92.8.

**2-(2H-1,2,3-Triazol-2-yl)benzoic Acid (5a).** Iodide **9a** (41.2 g, 0.152 mol) was dissolved in THF (300 mL), and the solution was cooled to –20 °C. Isopropylmagnesium chloride (80 mL as a 2 M solution in THF, 0.160 mol) was added slowly at –20 °C. The mixture was stirred for 20 min.  $\text{CO}_2$  (gas) was bubbled through the reaction mixture until no exotherm was observed. Temperature was kept between –20 °C and –10 °C. One M HCl (100 mL) was added to the mixture. THF was removed under reduced pressure. The residue was diluted with *i*PrOAc (300 mL) and  $\text{H}_2\text{O}$  (50 mL). Layers were separated, and the pH of the aqueous layer was adjusted to 1 with 2 M HCl (50 mL). The aqueous layer was extracted consecutively with *i*PrOAc (100 mL), TBME (100 mL), and DCM (300 mL). Organic layers were combined and concentrated under reduced pressure to give a yellow solid as crude material (25.8 g). The benzoic acid was recrystallized from toluene (200 mL) to yield a yellow solid. Yield: 22.3 g (78%). Purity (LC-MS method 1): 100% (220 nm),  $t_R$  0.81 min;  $[\text{M} + 1]^+ = 190$ , mp 138 °C (DSC);  $^1\text{H}$  NMR (500 MHz,  $\text{D}_6$ -DMSO)  $\delta$ : 13.08 (m, 1H), 8.09 (s, 2H), 7.77 (m, 2H), 7.71 (m, 1H), 7.60 (td,  $J_1 = 1.3$  Hz,  $J_2 = 7.5$  Hz, 1H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_6$ -DMSO)  $\delta$ : 168.1, 137.9, 136.8, 132.2, 130.0, 129.3, 128.6, 124.8.

**4,5-Dibromo-2-(4-methoxy-2-nitrophenyl)-2H-1,2,3-triazole (7b).** A mixture of 4-fluoro-3-nitroanisole **6b** (80 g, 0.453 mol), 4,5-dibromo-2H-1,2,3-triazole **10** (108 g, 0.476 mol),  $\text{K}_2\text{CO}_3$  (68.9 g, 0.499 mol), and DMF (560 mL) was heated to 120 °C for 21 h. The reaction mixture was cooled to 10 °C and diluted with  $\text{H}_2\text{O}$  (1.2 L). The resulting suspension was filtered, and the cake was washed with  $\text{H}_2\text{O}$  (200 mL). The product was dissolved in *i*PrOAc (1 L). The organic layer was washed with  $\text{H}_2\text{O}$  (700 and 500 mL) and evaporated under reduced pressure. To the residue was added *i*PrOH (500 mL). The resulting suspension was filtered and the off-white solid was dried under reduced pressure. Yield: 133 g (78%). Purity (LC-MS method 2): 100% (210 nm),  $t_R$  1.03 min, mp 118 °C (DSC);  $^1\text{H}$  NMR (500 MHz,  $\text{D}_6$ -DMSO)  $\delta$ : 7.91 (d,  $J = 8.9$  Hz, 1H), 7.74 (d,  $J = 2.8$  Hz, 1H), 7.48 (dd,  $J_1 = 2.8$  Hz,  $J_2 = 9.0$  Hz, 1H), 3.94 (s, 3H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_6$ -DMSO)  $\delta$ : 160.9, 144.5, 128.3, 127.8, 124.5, 120.0, 111.1, 57.2.

**5-Methoxy-2-(2H-1,2,3-triazol-2-yl)aniline Monosulfate (8b).** Nitro compound **7b** (100 g, 0.265 mol), NaOAc (76 g, 0.556 mol), and 10% Pd/C (50% water wet, 10.1 g) were suspended in EtOAc (1 L) and  $\text{H}_2\text{O}$  (100 mL). The reaction mixture was pressurized with nitrogen three times to 3 bar and two times with hydrogen to 3 bar. The mixture was heated to 50 °C and set under hydrogen (2 bar) for one hour. The reaction mixture was filtered at 23 °C. The cake was rinsed with  $\text{H}_2\text{O}$  (400 mL). Layers were separated, and the organic layer was washed with a 10% aqueous citric acid solution (400 mL) and with  $\text{H}_2\text{O}$  (500 mL). The organic layer was concentrated under reduced pressure to give an oil (52 g). The crude aniline was dissolved in *i*PrOH (350 mL), and conc.  $\text{H}_2\text{SO}_4$  (14.6 mL, 0.273 mol) was added below 40 °C. The suspension was cooled to 22 °C and filtered. The cake was washed with *i*PrOH (50 mL) and TBME (150 mL). The solid was dried under reduced pressure to obtain a white solid.

Yield: 70.4 g (89%). Purity (LC-MS method 2): 100% (210 nm),  $t_R$  0.71 min;  $[M + 1]^+ = 191$ , mp 216 °C (DSC);  $^1H$  NMR (500 MHz,  $D_2O$ )  $\delta$ : 7.97 (d,  $J = 1.3$  Hz, 2H), 7.75 (d,  $J = 9.0$  Hz, 1H), 7.03 (m, 2H), 3.83 (s, 3H),  $^{13}C$  NMR (125 MHz,  $D_6$ -DMSO)  $\delta$ : 160.1, 142.2, 135.0, 124.8, 119.5, 103.1, 101.4, 55.5.

**2-(2-Iodo-4-methoxyphenyl)-2H-1,2,3-triazole (9b).** Aniline **8b** (200 g, 0.694 mol) was dissolved in 2 M  $H_2SO_4$  (1.4 L) and cooled to  $-5$  °C. To the mixture was added a solution of sodium nitrite (62 g, 0.902 mol) in  $H_2O$  (600 mL) at  $-5$  to 0 °C. The mixture was stirred at 0 °C for 30 min and then added carefully to a solution of potassium iodide (161 g, 0.971 mol) in  $H_2O$  (700 mL) at 65 °C. The mixture was stirred at 60 °C for 20 min, cooled to 22 °C, and treated with a solution of sulfamic acid (27 g, 0.278 mol) in  $H_2O$  (120 mL). The mixture was extracted with *i*PrOAc (2 L). The organic layer was washed with a mixture of 2 N NaOH (500 mL) and 40% aqueous bisulfite solution (100 mL), 1 M HCl (50 mL) and  $H_2O$  (500 mL). The organic layer was concentrated to dryness under reduced pressure to yield 204 g of a red solid. The residue was dissolved in *i*PrOH (700 mL) at 70 °C and cooled to 2 °C. The suspension was filtered. The yellow solid was rinsed with *i*PrOH (150 mL) and dried under reduced pressure. Yield: 164 g (79%). Purity (LC-MS method 1): 100% (210 nm),  $t_R$  1.54 min;  $[M + 1]^+ = 302$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$ : 7.87 (s, 2H), 7.49 (d,  $J = 2.7$  Hz, 1H), 7.38 (d,  $J = 8.8$  Hz, 1H), 7.00 (dd,  $J_1 = 2.7$  Hz,  $J_2 = 8.8$  Hz, 1H), 3.87 (s, 3H),  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$ : 160.4, 136.8, 135.3, 128.3, 125.0, 114.5, 93.7, 55.9.

**5-Methoxy-2-(2H-1,2,3-triazol-2-yl)benzoic Acid (5b).** Iodide **9b** (200 g, 0.664 mol) was dissolved in THF (2 L) and cooled to 0 °C. Isopropylmagnesium chloride (350 mL as a 2 M solution in THF, 0.697 mol) was added at 0 °C. The mixture was cooled to  $-20$  °C, and  $CO_2$  (gas) was bubbled into the solution over 30 min. To the mixture was added 2 N HCl (600 mL) at 8 °C. THF was removed under reduced pressure at 60 °C (2.4 L solvent removed). The residue was extracted with TBME (1.6 L). The organic layer was washed with 1 M HCl (200 mL). The product was extracted into the aqueous layer with 1 M NaOH (600 and 200 mL). The aqueous layer was filtered over activated charcoal (15 g, DARCO), diluted with  $H_2O$  (200 mL), and treated with 32% aqueous HCl (160 mL). The resulting suspension was filtered and washed with  $H_2O$  (200 mL). The product was dried at 60 °C and reduced pressure to yield an orange solid. The obtained product can be crystallized from toluene or  $H_2O$ . Yield: 127 g (87%). Purity (LC-MS method 1): 100% (210 nm),  $t_R$  1.07 min;  $[M + 1]^+ = 220$ , mp 130 °C (DSC);  $^1H$  NMR (500 MHz,  $D_6$ -DMSO)  $\delta$ : 12.99 (bs, 1H), 8.02 (s, 2H), 7.65 (d,  $J = 8.8$  Hz, 1H), 7.26 (m, 2H), 3.87 (s, 3H),  $^{13}C$  NMR (125 MHz,  $D_6$ -DMSO)  $\delta$ : 167.5, 159.5, 136.2, 131.6, 130.4, 126.9, 117.5, 114.8, 56.3.

**4,5-Dibromo-2-(5-methyl-2-nitrophenyl)-2H-1,2,3-triazole (7c).** A mixture of 3-fluoro-4-nitrotoluene **6c** (1.367 kg, 8.81 mol), 4,5-dibromo-2H-1,2,3-triazole **10** (1.999 kg, 8.81 mol),  $K_2CO_3$  (1.340 kg, 9.69 mol), and DMF (11 L) was heated to 75 °C for 15 h. The reaction mixture was cooled to 22 °C, diluted with  $H_2O$  (18 L), and filtered. The product cake was washed with  $H_2O$  (4 L) and *i*PrOH (5 L). The solid was dried under reduced pressure to give an off white solid. Yield: 2811 g (88%). Purity (LC-MS method 1): 100% (210 nm),  $t_R$  1.88 min; mp 123 °C (DSC);  $^1H$  NMR (500 MHz,  $D_6$ -DMSO)  $\delta$ : 7.87 (d,  $J = 8.3$  Hz, 1H), 7.63 (d,  $J = 0.8$  Hz, 1H), 7.43 (dd,  $J_1$

$= 0.7$  Hz,  $J_2 = 8.3$  Hz, 1H), 2.54 (s, 3H),  $^{13}C$  NMR (125 MHz,  $D_6$ -DMSO)  $\delta$ : 146.4, 141.2, 132.0, 131.3, 128.4, 127.1, 126.0, 21.3.

**4-Methyl-2-(2H-1,2,3-triazol-2-yl)aniline Monosulfate (8c).** Nitro compound **7c** (300 g, 0.276 mol), NaOAc trihydrate (282 g, 2.07 mol), and 5% Pd/C (50% water wet, 30.9 g) were suspended in EtOAc (1.5 L). The reaction mixture was pressurized with nitrogen three times to 3 bar and two times with hydrogen to 3 bar. The mixture was heated to 40–50 °C and stirred under hydrogen (1 bar) in an autoclave for 2 h.

Five more batches with 300 g and one with 212 g were hydrogenated (total input of **7c**: 2.012 kg, 5.56 mol). The combined reaction mixtures were filtered over paper. The filtrate (ca. 10 L) was washed with  $H_2O$  (8 L), 1 M NaOH (4 L), and 50% aqueous NaOH (250 mL) and finally with  $H_2O$  ( $3 \times 2$  L). The organic layer was concentrated in a 30 L glass lined reactor at 80 °C under reduced pressure (ca. 9 L solvent was distilled off). *i*PrOH (12 L) was added to the residue. The solution was again concentrated under reduced pressure, and ca. 3 L solvent was removed. To the residue was added conc.  $H_2SO_4$  (573 g, 5.84 mol) below 50 °C. The suspension was cooled to 20 °C and filtered. The cake was washed with *i*PrOH (3 L). The product was dried at 60 °C to obtain a beige solid. Yield: 1.298 kg (86%). Purity (LC-MS method 2): 100% (210 nm),  $t_R$  0.65 min;  $[M + 1]^+ = 175$ , mp 219 °C (DSC);  $^1H$  NMR (500 MHz,  $D_6$ -DMSO)  $\delta$ : 8.22 (s, 2H), 7.73 (d,  $J = 1.1$  Hz, 2H), 7.59 (m, 4H), 7.31 (m, 1H), 7.25 (m, 1H), 2.36 (s, 3H),  $^{13}C$  NMR (125 MHz,  $D_6$ -DMSO)  $\delta$ : 136.7, 134.8, 130.1, 130.1, 127.4, 123.9, 123.1, 20.7.

**2-(2-Iodo-5-methylphenyl)-2H-1,2,3-triazole (9c).** Aniline **8c** (1553 g, 5.7 mol) was dissolved in 1 M aqueous  $H_2SO_4$  solution (11 L) and cooled to  $-5$  °C. To the mixture was added a solution of sodium nitrite (433 g, 6.27 mol) in  $H_2O$  (4 L) at  $-5$  to 0 °C. The mixture was stirred at 0 °C for 30 min and then added to a mixture of potassium iodide (1325 g, 7.99 mol) in  $H_2O$  (4 L) at 55–70 °C. The resulting dark mixture was stirred at 60 °C for 20 min, cooled to 20 °C, and treated with a solution of sulfamic acid (220 g, 2.28 mol) in  $H_2O$  (900 mL). The mixture was extracted with *i*PrOAc (13 L). The organic layer was washed with a mixture of 2 N NaOH (3.5 L) and 40% aqueous sodium bisulfite solution (330 g), and a mixture of 1 M HCl (280 mL) in  $H_2O$  (3.5 L). The organic layer was concentrated to dryness under reduced pressure at 60 °C to afford a brown oil. Yield: 1580 g (97%). Purity (LC-MS method 1): 91% (210 nm),  $t_R$  1.59 min;  $[M + 1]^+ = 286$ .

The crude product, together with a second batch (1411 g, 96%), was purified by distillation on a short path distillation equipment at 120 °C jacket temperature, feeding tank (70 °C), cooling finger (20 °C) and at a pressure of 0.004 mbar. Yield: 2.544 kg (78%). Purity (LC-MS method 1): 100% (210 nm),  $t_R$  1.59 min;  $[M + 1]^+ = 286$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$ : 7.85 (s, 2H), 7.81 (d,  $J = 8.1$  Hz, 1H), 7.30–7.30 (m, 1H), 6.98 (m, 1H), 2.33 (s, 3H),  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$ : 143.0, 140.0, 139.4, 135.5, 131.8, 128.5, 88.4, 20.8.

**4-Methyl-2-(2H-1,2,3-triazol-2-yl)benzoic Acid (5c).** Iodide **9c** (1250 g, 4.38 mol) was dissolved in THF (13 L) and cooled to 0 °C. Isopropylmagnesium chloride (2.2 L as a 2 M solution in THF, 4.38 mol) was added at 0 °C. The mixture was cooled to  $-25$  °C and  $CO_2$  (gas) was bubbled into the solution over 60 min until the exothermicity was ceased. Two N HCl (5 L) was added at 4 °C, and the mixture was concentrated under reduced pressure to remove 14.5 L solvent. The residue was

extracted with TBME (10 L). The organic layer was extracted with 1 M NaOH (6 and 3 L). The combined aqueous layers were treated with 32% aqueous HCl (1.23 L). The resulting suspension was filtered and washed with H<sub>2</sub>O (5 L). The yellow solid was dried at 60 °C and reduced pressure. Yield: 796 g (89%). Purity (LC-MS method 1): 100% (210 nm),  $t_R$  1.10 min;  $[M + 1]^+$  = 204, mp 125 °C (DSC); <sup>1</sup>H NMR (500 MHz, D<sub>6</sub>-DMSO)  $\delta$ : 12.90 (bs, 1H), 8.06 (s, 2H), 7.68 (d,  $J$  = 7.9 Hz, 1H), 7.56 (d,  $J$  = 0.5 Hz, 1H), 7.41 (ddd,  $J_1$  = 0.7 Hz,  $J_2$  = 1.6 Hz,  $J_3$  = 7.9 Hz, 1H), 2.44 (s, 3H), <sup>13</sup>C NMR (125 MHz, D<sub>6</sub>-DMSO)  $\delta$ : 167.9, 142.7, 138.2, 136.5, 130.2, 129.9, 126.2, 125.6, 21.2.

**4,5-Dibromo-2-(4-methyl-2-nitrophenyl)-2H-1,2,3-triazole (7d).** A mixture of 4-fluoro-3-nitrotoluene **6d** (90 g, 0.58 mol), K<sub>2</sub>CO<sub>3</sub> (80.2 g, 0.58 mol), 4,5-dibromo-2H-1,2,3-triazole **10** (132 g, 0.58 mol), and DMF (700 mL) was stirred at 85 °C for 20 h. After cooling to 22 °C, H<sub>2</sub>O (1.2 L) was added and the resulting yellowish suspension was filtered. The cake was rinsed with H<sub>2</sub>O (200 mL). The solid was stirred in *i*PrOH (500 mL), filtered, and dried at 60 °C under reduced pressure. Yield: 185.3 g (88%). Purity (LC-MS method 2): 98% (220 nm),  $t_R$  0.96 min; mp 155 °C (DSC); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.74 (d,  $J$  = 1.1 Hz, 1H), 7.69 (d,  $J$  = 8.2 Hz, 1H), 7.55 (ddd,  $J_1$  = 0.6 Hz,  $J_2$  = 1.8 Hz,  $J_3$  = 8.2 Hz, 1H), 2.53 (m, 3H), <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 143.1, 141.4, 133.8, 129.7, 127.9, 125.6, 125.5, 21.2.

**5-Methyl-2-(2H-1,2,3-triazol-2-yl)aniline Sulfate (8d).** Nitro compound **7d** (185 g, 0.51 mol) was suspended in EtOAc (900 mL) in an autoclave equipped with a hollow shaft stirrer. To the suspension was added NaOAc (105 g, 1.28 mol) and 5% Pd/C (50% water wet, 19 g). The reaction mixture was pressurized with nitrogen three times to 3 bar and two times with hydrogen to 3 bar. The mixture was hydrogenated at 30 °C jacket temperature at 1 bar pressure. After 90 min the hydrogen uptake stalled and triethylamine (140 mL, 1 mol) and 5% Pd/C (50% water wet, 5 g) were added and the reaction was continued until hydrogen (ca. 56.5 L) was consumed. The suspension was filtered and the cake was rinsed with H<sub>2</sub>O (1 L). 32% aqueous NaOH (20 mL) was added to reach pH 10, and layers were separated. The organic phase was washed twice with H<sub>2</sub>O (500 mL). The organic phase was concentrated to dryness at 60 °C to give a red oil as crude product (83.9 g). This oil was dissolved in *i*PrOH (1 L) and heated to 50 °C. Concentrated H<sub>2</sub>SO<sub>4</sub> (28.6 mL, 0.537 mol) was added. The thick white suspension was stirred overnight at 22 °C and then filtered. The cake was rinsed with *i*PrOH (300 mL). The obtained white solid was dried at 60 °C under reduced pressure. Yield: 119 g (86%). Purity (LC-MS method 2): 100% (210 nm),  $t_R$  0.70 min;  $[M + 1]^+$  = 175, mp 237 °C (DSC); <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O)  $\delta$ : 7.98 (s, 2H), 7.78 (d,  $J$  = 8.3 Hz, 1H), 7.38 (d,  $J$  = 8.4 Hz, 1H), 7.34 (d, 1H), 2.34 (s, 3H), <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O)  $\delta$ : 141.0, 136.7, 130.6, 130.2, 125.4, 123.5, 122.1, 20.0.

**2-(2-Iodo-4-methylphenyl)-2H-1,2,3-triazole (9d).** Aniline **8d** (80 g, 0.294 mol) was suspended in 1 M H<sub>2</sub>SO<sub>4</sub> (560 mL) and cooled to -5 °C. A solution of sodium nitrite (22.3 g, 0.323 mol) in H<sub>2</sub>O (240 mL) was added. The reaction mixture was stirred at 2 °C for 20 min. In another vessel potassium iodide (68.3 g, 0.411 mol) was dissolved in H<sub>2</sub>O (280 mL) at 85 °C. To this solution was added the diazonium solution over 20 min. Thirty min after the addition the reaction mixture was cooled to 30 °C. A solution of sulfamic acid (11.4 g, 0.118 mol) in H<sub>2</sub>O (50 mL) was added, and the mixture was stirred

for 10 min. *i*PrOAc (800 mL) was added followed by 2 N NaOH (180 mL) and a 40% aqueous solution of sodium bisulfite (17 g). The pH was adjusted to 12 with 32% aqueous NaOH (50 mL). Layers were separated, and the organic phase was washed with H<sub>2</sub>O (200 mL) and 1 M HCl (20 mL). The organic phase was concentrated to dryness to afford an orange solid as crude material (82 g). The crude product was dissolved in *i*PrOH (600 mL) at 70 °C. The solution was cooled to 5 °C, and *n*-heptane (200 mL) was added. The suspension was filtered, and the cake was rinsed with cold *i*PrOH (150 mL). The yellow solid was dried under reduced pressure at 65 °C. Yield: 67 g (80%). Purity (LC-MS method 2): 100% (210 nm),  $t_R$  0.83 min; mp 113 °C (DSC); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.89 (s, 2H), 7.85 (d,  $J$  = 1.0 Hz, 1H), 7.37 (m, 1H), 7.28–7.30 (m, 1H), 2.42 (s, 3H), <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 141.4, 140.9, 140.7, 135.4, 129.6, 127.3, 92.7, 20.7.

**5-Methyl-2-(2H-1,2,3-triazol-2-yl)benzoic Acid (5d).** Iodide **9d** (153 g, 0.54 mol) was dissolved in THF (1.5 L), and the solution was cooled to -5 °C. Isopropylmagnesium chloride (290 mL as a 2 M solution in THF, 0.58 mol) was added over 20 min. The solution was further cooled down to -25 °C, and CO<sub>2</sub> (gas) was bubbled into the reaction mixture over a period of 30 min. Two N HCl (400 mL) was added, and the mixture was concentrated at 60 °C under reduced pressure. To the residue was added TBME (1.4 L). Layers were separated, and the organic phase was washed with 1 M HCl (400 mL). The organic phase was extracted with 1 M NaOH (400 and 200 mL). The organic layer was discarded, and the combined basic aqueous phases were treated with activated charcoal (3 g, DARCO) for 10 min. The suspension was filtered over paper. To the filtrate was added 32% aqueous HCl (55 mL), and the resulting suspension was filtered. The cake was rinsed with H<sub>2</sub>O (150 mL). The solid was dried under reduced pressure at 60 °C. The benzoic acid (92.3 g) was crystallized from toluene (600 mL) to yield a yellow solid. Yield: 87.1 g (80%). Purity (LC-MS method 2): 100% (210 nm),  $t_R$  0.66 min;  $[M + 1]^+$  = 204, mp 172 °C; <sup>1</sup>H NMR (500 MHz, D<sub>6</sub>-DMSO)  $\delta$ : 12.99 (s, 1H), 8.05 (s, 2H), 7.63 (m, 1H), 7.58 (d,  $J$  = 1.5 Hz, 1H), 7.50–7.52 (m, 1H), 2.43 (s, 3H), <sup>13</sup>C NMR (125 MHz, D<sub>6</sub>-DMSO)  $\delta$ : 168.1, 139.2, 136.5, 135.8, 132.5, 130.3, 128.7, 124.8, 20.9.

**2,2'-(4-Nitro-1,3-phenylene) Bis(4,5-dibromo-2H-1,2,3-triazole) (12).** A mixture of 2,4-difluoronitrobenzene **11** (25 g, 0.157 mol), K<sub>2</sub>CO<sub>3</sub> (65.2 g, 0.471 mol), 4,5-dibromo-2H-1,2,3-triazole **10** (89.1 g, 0.393 mol), and DMF (250 mL) was stirred overnight at 50 °C. To the suspension was added H<sub>2</sub>O (500 mL) at 20 °C. The suspension was filtered and the cake was rinsed with H<sub>2</sub>O (500 mL), *i*PrOH (500 mL) and TBME (250 mL). The solid was dried under reduced pressure and 60 °C to afford an off-white product. Yield: 86.6 g (96%). Purity (LC-MS method 2): 100% (210 nm),  $t_R$  1.21 min; mp 247 °C (DSC); <sup>1</sup>H NMR (500 MHz, D<sub>6</sub>-DMSO)  $\delta$ : 8.42 (d,  $J$  = 2.3 Hz, 1H), 8.37 (d,  $J$  = 8.9 Hz, 1H), 8.30 (dd,  $J_1$  = 2.3 Hz,  $J_2$  = 8.9 Hz, 1H), <sup>13</sup>C NMR (125 MHz, D<sub>6</sub>-DMSO)  $\delta$ : 141.5, 141.2, 132.3, 130.1, 129.3, 128.5, 119.8, 115.4.

**2,4-Di(2H-1,2,3-triazol-2-yl)aniline (13).** Nitro compound **12** (50 g, 0.0873 mol), 10% Pd/C (50% water wet, 8.45 g), KOAc (42.8 g, 0.436 mol), EtOAc (500 mL), and H<sub>2</sub>O (44 mL) were charged into an autoclave equipped with a hollow shaft stirrer. The reaction mixture was pressurized with nitrogen three times to 3 bar and two times with hydrogen to 3 bar. The reaction mixture was stirred at 60 °C under

hydrogen (3 bar) for 3 h. The mixture was filtered over paper. The filtrate was washed with H<sub>2</sub>O (500 mL). The organic layer was separated and washed with 1 M NaOH (2 × 300 mL) and H<sub>2</sub>O (300 mL). The organic layer was dried over MgSO<sub>4</sub> and filtered. The filtrate was concentrated at 60 °C under reduced pressure. The residue was crystallized from *i*PrOH (300 mL), and a white solid was obtained. Yield: 15.8 g (80%). Purity (LC-MS method 2): 99% (210 nm), *t*<sub>R</sub> 0.80 min; [M + 1]<sup>+</sup> = 228; <sup>1</sup>H NMR (500 MHz, D<sub>6</sub>-DMSO) δ: 8.39 (d, *J* = 2.5 Hz, 1H), 8.19 (s, 2H), 8.05 (s, 2H), 7.82 (dd, *J*<sub>1</sub> = 2.5 Hz, *J*<sub>2</sub> = 8.9 Hz, 1H), 7.12 (d, *J* = 8.9 Hz, 1H), 6.43 (s, 2H), <sup>13</sup>C NMR (125 MHz, D<sub>6</sub>-DMSO) δ: 140.1, 136.1, 135.8, 129.6, 124.0, 119.7, 118.4, 113.4.

**2,2'-(4-Iodo-1,3-phenylene) Bis(2H-1,2,3-triazole) (14).** Aniline **13** (5 g, 0.022 mol) was suspended in 2 M HCl (50 mL) and acetonitrile (50 mL). The suspension was cooled to 5 °C. A solution of sodium nitrite (1.67 g, 0.024 mol) in H<sub>2</sub>O (10 mL) was added. The reaction mixture was warmed to 15 °C. In another flask, potassium iodide (11 g, 0.066 mol) was dissolved in H<sub>2</sub>O (12.6 mL) at 70 °C. The first solution was added dropwise to the potassium iodide solution. The reaction mixture was stirred at 70 °C for 20 min. The mixture was cooled to 20 °C. Sulfamic acid (0.214 g, 0.0022 mol) was added to the mixture as well as 40% bisulfite solution (10 mL). Layers were separated, and the aqueous layer was extracted with *i*PrOAc (2 × 50 mL). Organic layers were combined and washed with H<sub>2</sub>O (2 × 50 mL). The organic layer was concentrated under reduced pressure to yield a yellow solid as crude material (7.2 g). The solid was recrystallized from *i*PrOH (70 mL). Yield: 6 g (81%). Purity (LC-MS method 2): 100% (210 nm), *t*<sub>R</sub> 0.92 min; mp 132 °C (DSC); <sup>1</sup>H NMR (500 MHz, D<sub>6</sub>-DMSO) δ: 8.27 (d, *J* = 8.6 Hz, 1H), 8.21 (m, 4H), 8.11 (d, *J* = 2.5 Hz, 1H), 7.97 (dd, *J*<sub>1</sub> = 2.5 Hz, *J*<sub>2</sub> = 8.6 Hz, 1H), <sup>13</sup>C NMR (125 MHz, D<sub>6</sub>-DMSO) δ: 143.9, 142.1, 140.0, 137.9, 137.0, 121.5, 117.5, 92.2.

**2,4-Di(2H-1,2,3-triazol-2-yl)benzoic Acid (15a).** Iodide **14** (10 g, 0.030 mol) was dissolved in THF (100 mL), and the solution was cooled to 3 °C. Isopropylmagnesium chloride (15.6 mL as a 2 M solution in THF, 0.031 mol) was added at 5 °C. The mixture was cooled to -25 °C. CO<sub>2</sub> (gas) was bubbled into the reaction mixture, which was then stirred for one hour at -20 °C. Two M HCl (40 mL) was added. THF was removed under reduced pressure. The residue was diluted with *i*PrOAc (100 mL). Layers were separated, and the organic layer was washed with 1 M HCl (100 mL) and extracted with 1 M KOH (2 × 30 mL). To the combined aqueous layers was added conc. HCl until a pH of 1 was reached at 0 °C. The suspension was filtered. The cake was rinsed with H<sub>2</sub>O (100 mL) and dried under reduced pressure at 55 °C to give an off-white solid. Yield: 7.33 g (97%). Purity (LC-MS method 2): 100% (210 nm), *t*<sub>R</sub> 0.70 min; [M + 1]<sup>+</sup> = 257, mp 187 °C (DSC); <sup>1</sup>H NMR (500 MHz, D<sub>6</sub>-DMSO) δ: 13.31 (bs, 1H), 8.37 (d, *J* = 2.1 Hz, 1H), 8.26 (s, 2H), 8.21 (dd, *J*<sub>1</sub> = 2.1 Hz, *J*<sub>2</sub> = 8.5 Hz, 1H), 8.18 (s, 2H), 7.97 (d, *J* = 8.5 Hz, 1H), <sup>13</sup>C NMR (125 MHz, D<sub>6</sub>-DMSO) δ: 167.5, 141.1, 138.7, 138.2, 137.4, 132.1, 127.2, 118.3, 113.9.

**2,4-Di(2H-1,2,3-triazol-2-yl)benzaldehyde (15b).** Iodide **14** (10 g, 0.0296 mol) was dissolved in THF (100 mL), and the solution was cooled to -2 °C. Isopropylmagnesium chloride (15.6 mL as a 2 M solution in THF, 0.031 mol) was added at -4 °C. DMF (4.58 mL, 0.059 mol) was added, and the red solution was stirred at -2 °C for 30 min and then at 20 °C for 1.5 h. Two M HCl (40 mL) was added. THF was

distilled off under reduced pressure. The residue was diluted with DCM (600 mL) and layers were separated. The organic layer was washed with 1 M HCl (100 mL) and H<sub>2</sub>O (100 mL), dried with MgSO<sub>4</sub>, filtered, and concentrated to give 6.86 g of an off-white solid. The product was recrystallized from acetone (75 mL), and a white solid was obtained. Yield: 6.47 g (91%); Purity (GC-MS): 100%, *t*<sub>R</sub> 4.46 min; [M + 1]<sup>+</sup> = 241, mp 211 °C (DSC); <sup>1</sup>H NMR (500 MHz, D<sub>6</sub>-DMSO) δ: 10.27 (d, *J* = 0.7 Hz, 1H), 8.57 (d, *J* = 2.1 Hz, 1H), 8.35 (s, 2H), 8.31 (s, 2H), 8.27 (ddd, *J*<sub>1</sub> = 0.7 Hz, *J*<sub>2</sub> = 2.1 Hz, *J*<sub>3</sub> = 8.6 Hz, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), <sup>13</sup>C NMR (125 MHz, D<sub>6</sub>-DMSO) δ: 190.1, 142.9, 141.6, 138.6, 138.6, 131.4, 127.2, 118.1, 112.6.

**2,2'-(2-Nitro-1,3-phenylene) Bis(4,5-dibromo-2H-1,2,3-triazole) (17).** A mixture of 4,5-dibromo-2H-1,2,3-triazole **10** (119 g, 0.525 mol), 2,6-difluoronitrobenzene **16** (38 g, 0.239 mol), K<sub>2</sub>CO<sub>3</sub> (72.6 g, 0.525 mol), and DMF (250 mL) was stirred at 90 °C overnight. The suspension was cooled to 22 °C, and H<sub>2</sub>O (1.2 L) was added. The brown suspension was filtered, and the cake was rinsed with H<sub>2</sub>O (1 L) and *i*PrOH (500 mL). The solid was dried under reduced pressure to give a light green solid. Yield: 136 g (99%). Purity (LC-MS method 2): 95% (210 nm), *t*<sub>R</sub> 1.17 min; mp 235 °C (DSC); <sup>1</sup>H NMR (500 MHz, D<sub>6</sub>-DMSO) δ: 8.22 (m, 2H), 8.08 (dd, *J*<sub>1</sub> = 8.7 Hz, *J*<sub>2</sub> = 7.9 Hz, 1H), <sup>13</sup>C NMR (125 MHz, D<sub>6</sub>-DMSO) δ: 135.3, 134.1, 131.2, 129.7, 126.4.

**2,6-Di(2H-1,2,3-triazol-2-yl)aniline (18).** Nitro compound **17** (82 g, 0.143 mol), 10% Pd/C (50% water wet, 13.9 g), KOAc (70.3 g, 0.716 mol), EtOAc (1.0 L), and H<sub>2</sub>O (72 mL) were charged into an autoclave equipped with a hollow shaft stirrer. The reaction mixture was pressurized with nitrogen three times to 3 bar and two times with hydrogen to 3 bar. The mixture was stirred at a jacket temperature of 60 °C under hydrogen (3 bar) for one hour. The mixture was filtered over paper. The cake was rinsed with EtOAc (300 mL). The layers were separated. The organic layer was washed with 16% aqueous NaOH (100 mL) and H<sub>2</sub>O (2 × 100 mL). The organic layer was filtered through a Whatman filter (4.5 μm). The filtrate was concentrated to dryness under reduced pressure to afford a yellow solid (33.7 g). The aniline **17** was crystallized from *i*PrOH (250 mL) to yield a white solid. Yield: 28 g (86%). Purity (LC-MS method 2): 98% (210 nm), *t*<sub>R</sub> 0.82 min; [M + 1]<sup>+</sup> = 228, mp 84 °C (DSC), <sup>1</sup>H NMR (500 MHz, D<sub>6</sub>-DMSO) δ: 8.20 (s, 4 H), 7.78 (d, *J* = 8.1 Hz, 2 H), 6.92 (t, *J* = 8.1 Hz, 1 H), 6.58 (brs, 2 H), <sup>13</sup>C NMR (125 MHz, D<sub>6</sub>-DMSO) δ: 136.1, 134.2, 127.0, 124.3, 116.2.

**2,2'-(2-Iodo-1,3-phenylene) Bis(2H-1,2,3-triazole) (19).** Aniline **18** (10 g, 0.044 mol) was suspended in 2 M HCl (50 mL) and MeCN (50 mL). The suspension was cooled to 0 °C, and a solution of sodium nitrite (3.3 g, 0.048 mol) in H<sub>2</sub>O (20 mL) was added. The yellow solution was stirred for 1 h at 0 °C. In another flask, potassium iodide (21.9 g, 0.132 mol) was dissolved in H<sub>2</sub>O (100 mL) at 70 °C. The diazonium salt solution was added to this solution at an external temperature of 75 °C. The mixture was cooled to 22 °C. Sulfamic acid (0.44 g, 0.004 mol), a 40% aqueous solution of sodium bisulfite (6 mL), and *i*PrOAc (200 mL) was added. The layers were separated. The organic layer was washed with H<sub>2</sub>O (2 × 100 mL). The organic layer was concentrated under reduced pressure to yield a yellow solid (14.5 g). The product was crystallized from *i*PrOH (100 mL). Yield: 13.6 g (91%). Purity (LC-MS): 100%, *t*<sub>R</sub> 0.77 min; [M + 1]<sup>+</sup> = 339, mp 144 °C (DSC); <sup>1</sup>H NMR (500 MHz, D<sub>6</sub>-DMSO) δ: 8.19 (m, 4H),

7.76 (m, 3H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$ : 145.1, 136.8, 130.5, 129.6, 97.9.

**2,6-Di(2H-1,2,3-triazol-2-yl)benzoic Acid (20a).** Iodide **19** (6.6 g, 0.020 mol) was dissolved in THF (66 mL), and the solution was cooled to 3 °C. Isopropylmagnesium chloride (10.3 mL as a 2 M solution in THF, 0.021 mol) was added at 5 °C. The mixture was stirred for 5 min. The reaction mixture was cooled to -25 °C.  $\text{CO}_2$  (gas) was bubbled into the reaction mixture, which was then stirred for one hour at -20 °C. Two M HCl (25 mL) was added, and THF was removed under reduced pressure. The residue was diluted with *i*PrOAc (100 mL). Layers were separated, and the organic layer was washed with 1 M HCl (100 mL) and extracted with 1 M KOH (2 × 20 mL). To the combined aqueous layers was added conc. HCl until a pH of 1 was reached at 0 °C. The suspension was filtered. The cake was rinsed with  $\text{H}_2\text{O}$  (50 mL) and dried at 55 °C under reduced pressure to give an off-white solid. Yield: 4.34 g (87%). Purity (LC-MS method 2): 99% (210 nm),  $t_{\text{R}}$  0.59 min;  $[\text{M} + 1]^+ = 257$ , mp 141 °C (DSC);  $^1\text{H}$  NMR (500 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$ : 13.22 (br s, 1H), 8.16 (s, 4H), 7.95 (d,  $J = 0.6$  Hz, 1H), 7.94 (s, 1H), 7.84 (dd,  $J_1 = 7.5$  Hz,  $J_2 = 8.7$  Hz, 1H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$ : 165.5, 137.9, 137.3, 131.6, 124.6, 124.0.

**2,6-Di(2H-1,2,3-triazol-2-yl)benzaldehyde (20b).** Iodide **19** (6.47 g, 0.019 mol) was dissolved in THF (65 mL), and the solution was cooled to -6 °C. Isopropylmagnesium chloride (10 mL as a 2 M solution in THF, 0.020 mol) was added at -6 to 0 °C. The mixture was stirred for 5 min. DMF (2.96 mL, 0.038 mol) was added. The mixture was warmed to 22 °C and stirred for two hours. The reaction mixture was warmed to 40 °C. After 1.5 h, additional DMF (2.96 mL, 0.038 mol) was added and the reaction mixture was stirred for 1.5 h. The mixture was quenched with 2 M HCl (25 mL), and THF was evaporated. The residue was diluted with *i*PrOAc (100 mL), and layers were separated. The organic layer was washed with 1 M HCl (100 mL) and  $\text{H}_2\text{O}$  (100 mL), and dried over  $\text{MgSO}_4$ . The filtrate was concentrated under reduced pressure to afford 4.68 g of an orange solid as crude material. The crude benzaldehyde was suspended in *i*PrOH (55 mL) and filtered. The recovered product (3.3 g) was again suspended in acetone (50 mL) and filtered. The isolated solid was discarded. The mother liquor was cooled to 0 °C and filtered. The product was dried under reduced pressure at 60 °C. Yield: 1.66 g (36%). Purity (GC-MS): 100%,  $t_{\text{R}}$  4.42 min;  $[\text{M} + 1]^+ = 240$ , mp 145 °C (DSC);  $^1\text{H}$  NMR (500 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$ : 10.51 (s, 1H), 8.22 (s, 4H), 8.07 (d,  $J = 8.2$  Hz, 2H), 7.91 (dd,  $J_1 = 7.8$  Hz,  $J_2 = 8.5$  Hz, 1H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$ : 165.5, 137.9, 137.3, 131.6, 131.4, 124.6.

**2,2',2''-(2-Nitrobenzene-1,3,5-triyl) Tris(4,5-dibromo-2H-1,2,3-triazole) (22).** A mixture of 4,5-dibromo-2H-1,2,3-triazole **10** (112 g, 0.494 mol),  $\text{K}_2\text{CO}_3$  (68.3 g, 0.494 mol), 2,4,6-trifluoronitrobenzene **21** (25 g, 0.141 mol), and DMF (250 mL) was stirred at 70 °C overnight. The mixture was cooled to 22 °C and  $\text{H}_2\text{O}$  (500 mL) was added. The resulting suspension was filtered, and the cake was rinsed with *i*PrOH (500 mL) and TBME (250 mL). The beige solid was dried under reduced pressure. Yield: 107 g (95%). Purity (LC-MS method 2): 100% (220 nm),  $t_{\text{R}}$  1.33 min;  $^1\text{H}$  NMR (500 MHz,  $\text{D}_7\text{-DMF}$ )  $\delta$ : 8.74 (s, 2H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_7\text{-DMF}$ )  $\delta$ : 140.0, 133.1, 132.6, 130.2, 130.0, 113.8.

**2,4,6-Tri(2H-1,2,3-triazol-2-yl)aniline (23).** Nitro compound **22** (50 g, 0.063 mol), 10% Pd/C (50% water wet, 10.4 g), KOAc (43.1 g, 0.439 mol), EtOAc (700 mL), and

$\text{H}_2\text{O}$  (50 mL) were charged into an autoclave equipped with hollow shaft stirrer. The reaction mixture was pressurized with nitrogen three times to 3 bar and two times with hydrogen to 3 bar. The reaction mixture was stirred at 60 °C under hydrogen (3 bar) for one hour. The reaction mixture was cooled to 22 °C and filtered over paper. The cake was washed with  $\text{H}_2\text{O}$  (100 mL). The cake was suspended in TFA (300 mL). The suspension was filtered over Celite (50 g). The filtrate was concentrated under reduced pressure. The residue was diluted with *i*PrOH (200 mL). The resulting suspension was filtered, and the product was rinsed with *i*PrOH (50 mL). The solid was dried under reduced pressure at 60 °C. Yield: 12.8 g (69%). Purity (LC-MS method 2): 100% (210 nm),  $t_{\text{R}}$  0.95 min;  $[\text{M} + 1]^+ = 295$ , mp 276 °C (DSC);  $^1\text{H}$  NMR (500 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$ : 8.48 (s, 2H), 8.30 (s, 4H), 8.14 (s, 2H), 7.11 (br s, 2H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$ : 136.8, 136.6, 132.9, 128.7, 126.7, 113.5.

**2,2',2''-(2-Iodobenzene-1,3,5-triyl) Tris(2H-1,2,3-triazole) (24).** Aniline **23** (31.5 g, 0.107 mol) was suspended in 2 M HCl (315 mL) and acetonitrile (315 mL). The suspension was cooled to 5 °C. A solution of sodium nitrite (9.59 g, 0.139 mol) in  $\text{H}_2\text{O}$  (63 mL) was added at 5–7 °C, and the suspension was warmed up to 22 °C. In another flask, potassium iodide (53.3 g, 0.321 mol) was dissolved in  $\text{H}_2\text{O}$  (315 mL) at 58–68 °C. The diazonium salt solution was added slowly to this solution. The reaction mixture was stirred 10 min at 65 °C. The mixture was cooled to 22 °C. Sulfamic acid (4.15 g, 0.0428 mol) and *i*PrOAc (300 mL) were added. The mixture was filtered over Celite, and layers were separated. The organic layer was washed with a mixture of 2 M NaOH (250 mL) and 40% aq. sodium bisulfite solution (50 mL), 1 M HCl (300 mL), and  $\text{H}_2\text{O}$  (300 mL). The organic layer was concentrated to dryness to afford an orange solid as crude material (34.9 g, 81%). The crude product was combined with two other batches, which were produced in a similar fashion (1.2 g + 11.7 g) and recrystallized in *i*PrOH (580 mL). Yield: 46.2 g (79%, calculated from 42.5 g aniline **23** (0.144 mol)). Purity (LC-MS method 2): 98%,  $t_{\text{R}}$  0.9 min;  $[\text{M} + 1]^+ = 406$ , mp 168 °C (DSC);  $^1\text{H}$  NMR (500 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$ : 8.27 (m, 8 H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$ : 145.9, 140.0, 138.5, 137.3, 118.3, 94.5.

**2,4,6-Tri(2H-1,2,3-triazol-2-yl)benzoic Acid (25a).** Iodide **24** (8 g, 0.020 mol) was dissolved in THF (80 mL), and the solution was cooled to 4 °C. Isopropylmagnesium chloride (10.4 mL as a 2 M solution in THF, 0.021 mol) was added at 5 °C and the mixture was stirred for 5 min. The mixture was cooled to -25 °C.  $\text{CO}_2$  (gas) was bubbled into the reaction mixture which was then stirred for one hour at -20 °C. Two M HCl (25 mL) was added, and THF was removed under reduced pressure. To the residue was added 1 M KOH until pH = 14 was reached. The suspension was cooled to 0 °C and acidified to pH = 1 with 32% aqueous HCl. The suspension was filtered. The cake was rinsed with  $\text{H}_2\text{O}$  (50 mL) and dried at 55 °C under reduced pressure to give a white solid. Yield: 6.19 g (97%). Purity (LC-MS method 2): 100%,  $t_{\text{R}}$  0.73 min;  $[\text{M} + 1]^+ = 324$ , mp 380 °C (DSC);  $^1\text{H}$  NMR (500 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$ : 13.5 (bs, 1H), 8.52 (s, 2H), 8.31 (s, 2H), 8.25 (s, 4H),  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_6\text{-DMSO}$ )  $\delta$ : 165.0, 140.1, 138.8, 138.5, 137.9, 121.3, 112.8.

**2,4,6-Tri(2H-1,2,3-triazol-2-yl)benzaldehyde (25b).** Iodide **24** (8.5 g, 0.021 mol) was dissolved in THF (85 mL), and the solution was cooled to -5 °C. Isopropylmagnesium chloride (11 mL as a 2 M solution in THF, 0.022 mol) was added at -5

°C. The suspension was stirred at  $-2$  °C for 10 min. DMF (3.25 mL, 0.042 mol) was added at  $-10$  °C and the mixture was stirred at 22 °C for 4 h. The reaction was quenched with 2 M HCl (22 mL). THF was removed under reduced pressure, and the residue was filtered. The cake was rinsed with 1 M HCl (50 mL) and with H<sub>2</sub>O (50 mL). The product was dried at 60 °C under reduced pressure to afford 5.3 g of a yellow solid with a purity of 93% a/a. The product was suspended in acetonitrile (640 mL) at reflux. The suspension was filtered at 22 °C, and the mother liquor was concentrated to dryness to afford 620 mg of a yellow solid. Yield: 620 mg (9.6%). Purity (LC-MS method 2): 100%,  $t_R$  0.94 min;  $[M + 1]^+ = 308$ , mp 253 °C (DSC); <sup>1</sup>H NMR (500 MHz, D<sub>6</sub>-DMSO)  $\delta$ : 10.59 (s, 1H), 8.61 (s, 2H), 8.33 (s, 2H), 8.28 (s, 4H), <sup>13</sup>C NMR (125 MHz, D<sub>6</sub>-DMSO)  $\delta$ : 190.5, 141.0, 139.4, 138.6, 138.1, 122.8, 110.6.

**1,3,5-Tri(2H-1,2,3-triazol-2-yl)benzene (25c).** Iodide **24** (9 g, 0.022 mol) was dissolved in THF (90 mL), and the solution was cooled down to 3 °C. Isopropylmagnesium chloride (11.7 mL as a 2 M solution in THF, 0.0233 mol) was added at 3 °C. The suspension was stirred for 15 min. The reaction mixture was poured into a sat. solution of NH<sub>4</sub>Cl (100 mL) and ice (50 g). The suspension was filtered and the cake rinsed with THF (20 mL) and H<sub>2</sub>O (20 mL). The filtrate was concentrated to remove THF. The suspension was filtered and the solid was combined with the first solid cake and dried to give an off-white product. Yield: 6.19 g (100%). Purity (LC-MS method 3): 99.8% (254 nm),  $t_R$  10.00 min;  $[M + 1]^+ = 280$ , mp 398 °C (DSC); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub> and TFA)  $\delta$ : 8.75 (s, 3H), 8.05 (s, 6H), <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub> and TFA)  $\delta$ : 141.0, 136.8, 109.2.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.oprd.8b00349](https://doi.org/10.1021/acs.oprd.8b00349).

Experimental procedures and analytical data for compounds **2** and **3**; NMR, DSC, and X-ray powder diffraction for other compounds as well (PDF)

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### Notes

The authors declare no competing financial interest.

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