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Novel and Practical Industrial Process Scale-Up of 5-Bromo-2-chloro-4-(methoxycarbonyl) benzoic acid, a Key Intermediate in the Manufacturing of Therapeutic SGLT2 Inhibitors

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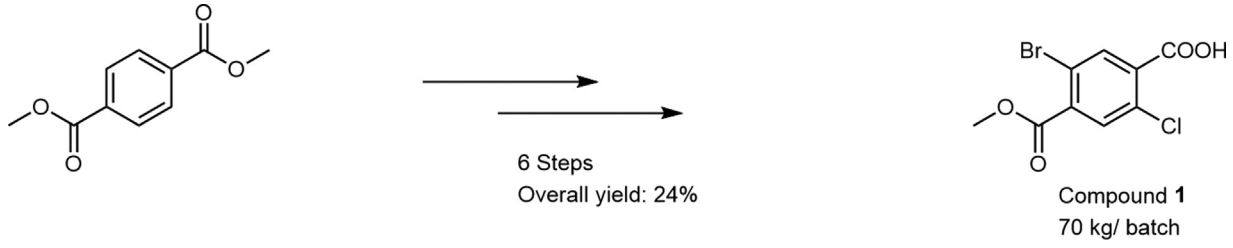

Abstract

5-Bromo-2-chloro-4-(methoxycarbonyl)benzoic acid (**1**) is a key intermediate for the synthesis of a family of promising SGLT2 inhibitors currently in preclinical and phase I studies for diabetes therapy. In this investigation, cheap, easily available dimethyl terephthalate was used as the raw starting material, and compound **1** was prepared effectively in six steps, including nitration, hydrolysis, hydrogenation, esterification, bromination, and diazotization. The preparation was run successfully on approximately 70 kg/batch with the total yield of 24%. This practical process was demonstrated to be scalable with a great yield and significant cost reduction.

Keywords

- 5-bromo-2-chloro-4-(methoxycarbonyl) benzoic acid
- SGLT2 inhibitors
- practical process
- scale up

Introduction

Diabetes is a serious, chronic disease that occurs either when the pancreas does not produce enough insulin (a hormone that regulates blood sugar, or glucose) or when the body cannot effectively use the insulin it produces. Diabetes is an important public health problem, one of four priority noncommunicable diseases targeted for action by world leaders. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades. Although there are antidiabetic drugs on the market, hyperglycemia is still clinically hard to be controlled. So, it is necessary to develop new antidiabetic drugs with novel targets and mechanisms. Sodium-glucose

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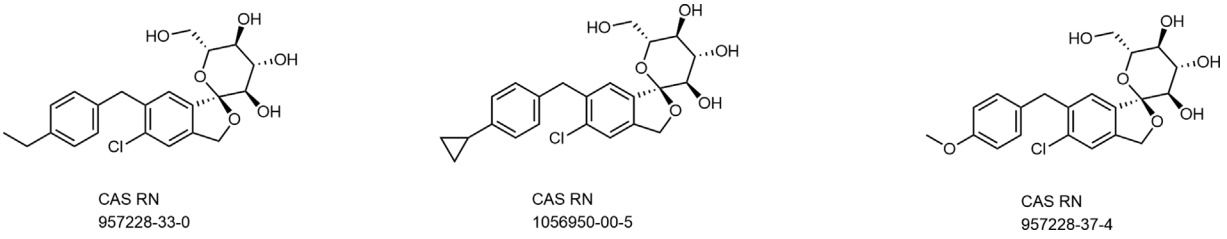


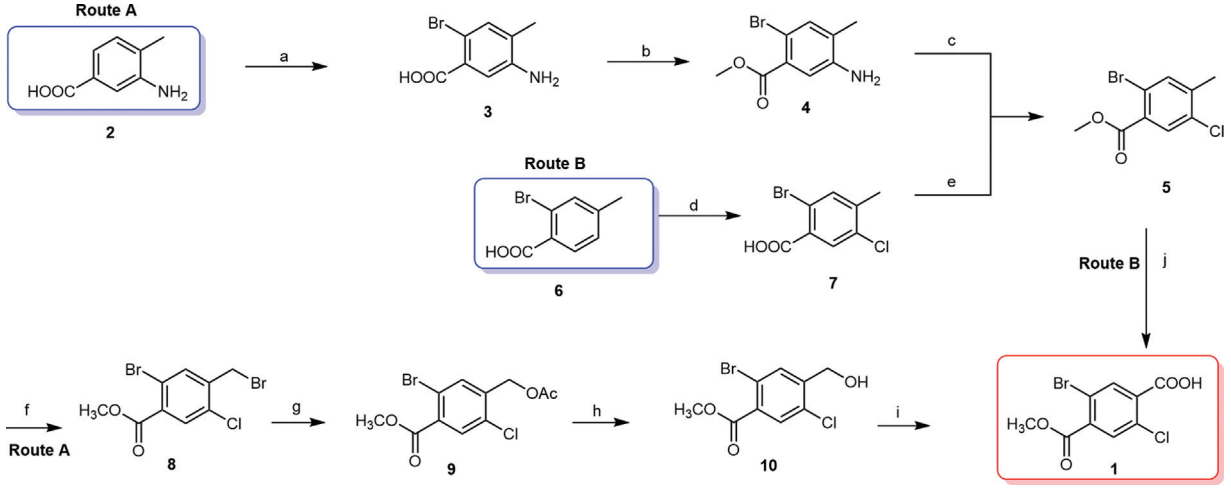
Fig. 1 SGLT-2 inhibitor drugs under investigation.

cotransporter-2 (SGLT2) inhibitors are a new class of diabetes treatment drugs. Mechanistically, they remove glucose from the urine by inhibiting the reabsorption of near-curved renal tubular glucose, which reduces blood glucose levels without depending on insulin. Besides, they could also reduce body weight, lower blood pressure, and have broad application prospects.[1]

In recent years, several research teams have devoted to the study of structure–activity relationship of SGLT2 inhibitors, and discovered that bromoaryls are active fragments to synthesize various promising candidate compounds as highly effective SGLT2 inhibitors.[2–5] Among these inhibitors, 5-bromo-2-chloro-4-(methoxycarbonyl)benzoic acid (**1**) is a key intermediate in high demand that is utilized for developing SGLT-2 inhibitors (►**Fig. 1**).[6] The known synthetic routes of compound **1** are all in small scale, in which the operation is complex and unpractical for industrial scale-up. Therefore, it is necessary to develop a feasible synthetic route and industrialized preparation method with high yield, low cost, and easy scale-up.

The reported synthetic route of compound **1** is shown in **Scheme 1**.[7–9] Route A: 3-amino-4-toluic acid (**2**) is used as the starting material, the key intermediate **5** is obtained in three steps including aryl bromination, esterification, and Sandmeyer reaction. Route B: 2-bromo-4-methylbenzoic acid (**6**) goes through aromatic ring chlorination and esterification to prepare intermediate **5**. The key intermediate **5** is oxidized with different oxidizing reagents and related conditions to obtain the target **1.** These preparation methods have their deficits such as the expensive starting materials and undesirable oxidation efficiency, which is difficult to meet the market demand for industrialized mass production.

To develop an industrial process of intermediate **1**, we conducted retro-synthesis analysis based on structural characteristics of the compound. Specifically, compound **1** can be synthesized from compound **12** through compound **11** (►**Fig. 2**), based on the existing literature.[10–13] Herein, a new synthetic route (**Scheme 2**) of compound **1** was designed and explored. Compound **11** is new compound that has not been reported in the literature.



Scheme 1 The reported synthetic route of **1**. Reagents and conditions: (a) NBS, DMF; (b) $SOCl_2$, MeOH; (c) $NaNO_2$, CuCl, HCl, dioxane; (d) NCS, CCl_4; (e) $SOCl_2$, MeOH; (f) NBS, AIBN, CCl_4; (g) AcONa, DMF; (h) LiOH·H_2O, THF, MeOH, H_2O; (i) PDC, DMF; (j) $KMnO_4$, 18-crown-6, *t*-BuOH, H_2O or 10% NaClO, TBAB, $RuCl_3 \cdot 3H_2O$, DCE, pH = 9.

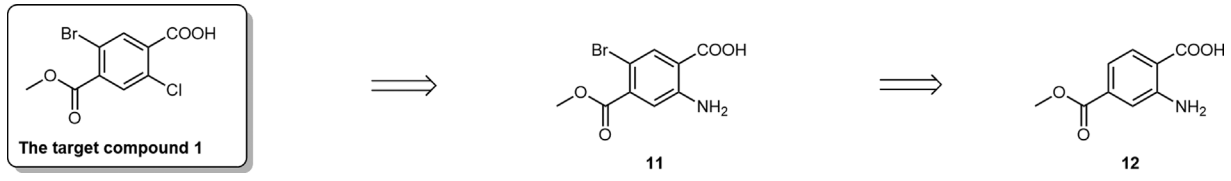
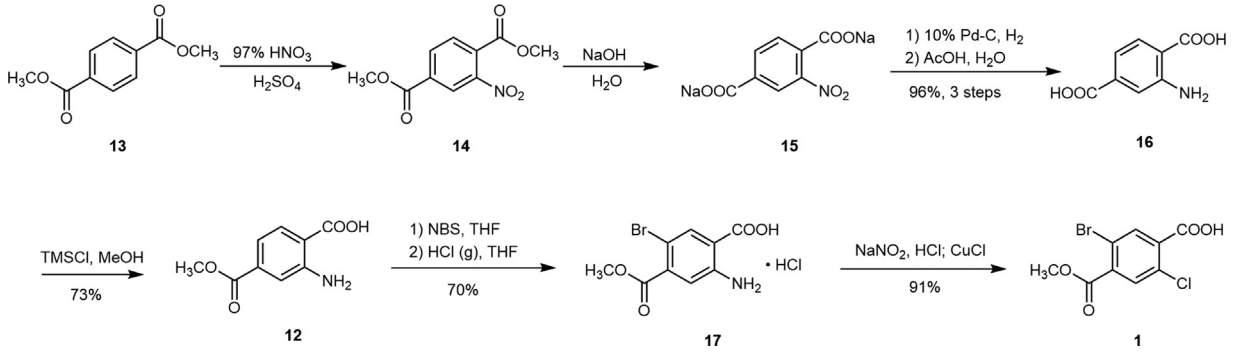
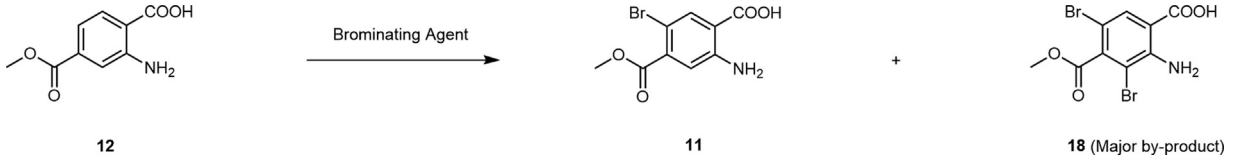


Fig. 2 Retrosynthetic analysis of compound **1** through a nonoxidative route.



Scheme 2 The novel synthesis route of **1**.



Scheme 3 The formation of product **11** and impurity **18**.

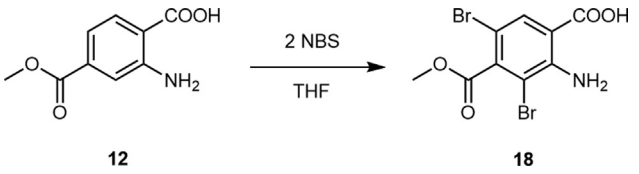
Utilizing cheap and commercially available dimethyl terephthalate (**13**) as a raw material, compound **14** was obtained by nitrification in the mixture of HNO_3 and H_2SO_4. Then, **14** was hydrolyzed with NaOH and the product **16** is a solution of disodium salt. Direct catalytic hydrogenation of **15** without separation could easily provide **16**, which reacted with TMSCl in MeOH to yield monoesterified intermediate **12**. Compound **12** was brominated to obtain intermediate **11**, which formed salt **17** (**11**·HCl) with hydrogen chloride gas. The target compound **1** was synthesized by the Sandmeyer reaction from compound **17**.

After the optimization of the above synthetic route, 70 kg of compound **1** was prepared with high yield and purity, and this large-scale production is a feasible and low-cost new route.

Results and Discussion

In this new synthetic route of compound **1**, compound **11** and its hydrochloride salt **17** are new compounds that have not been reported in the literature; it is the focus of this work. Compound **11** can be prepared by bromination of **12**, but it also produces dibromo by-product **18** (**Scheme 3**), which is difficult to separate from compound **11** and unavoidably decreases the purity of final product. In this article, excess amount of *N*-bromosuccinimide (NBS) was used to react with compound **12** to prepare the main by-product **18**, which was used as a reference substance for screening reaction conditions (**Scheme 4**). Both Br_2 and NBS were used as brominating agents in tetrahydrofuran, respectively, and reaction conditions were investigated and optimized regarding the amounts of bromination reagents and reaction temperature (►**Table 1**).

The results showed that: (1) the proportion of dibromo impurity increased significantly as the reaction temperature increased (►**Table 1**, entries 1–7); (2) under the same equiv., NBS was a preferable brominating agent due to less formation of dibromo impurities **18** (►**Table 1**, entries 2 and 7); (3) using 1.22 equiv. of NBS gave the target compound **11** with the highest yield and purity (►**Table 1**, entries 7–10).



Scheme 4 The targeted synthesis of **18**.

In summary, it was found that 1.22 equiv. of NBS was used as the brominating agent to carry out the reaction at 0–10°C and provided the best result. After the reaction, the solvent was removed by concentration under reduced pressure to obtain a mixed solid of product **11** and succinimide. The purification of **11** was achieved by refluxing the mixture in acetonitrile to remove succinimide because of its high solubility in acetonitrile.

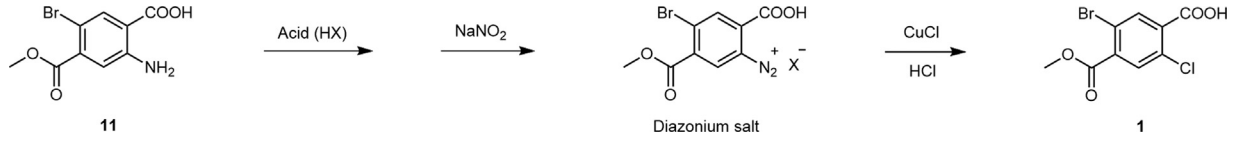
Based on our knowledge, product **1** prepared from compound **11** by diazotization has not been reported in the literature. Theoretically, **1** could be prepared by diazotization, followed by Sandmeyer reaction. For the Sandmeyer reaction, the corresponding diazonium salt needed to be prepared first, and then the reaction was performed under the catalysis of cuprous salt to obtain the product (**Scheme 5**). Several commonly available industrial systems for the preparation of diazonium salts to generate compound **1** by Sandmeyer reaction were investigated.[14–16] The results showed that the yield of the reaction was relatively low (25–46%), which could not meet the requirement of the practical application of scale-up (►**Table 2**).

After carefully studying and analyzing the reaction process of diazonium–Sandmeyer, we found that the yield of the reaction was limited by the diazonium salt formation. The more of the diazonium salts was produced in the solvent, the higher yield would be obtained after work-up. Otherwise,

Table 1 Screening conditions of brominating reaction

Entry	Brominating agent	Brominating agent (equiv.)	Temp (°C)	11 (%)[a]	18 (%)[a]	12 (%)[a]
1	Br_2	1	−20 to −10	92	1.1	5.5
2	Br_2	1	−10 to 0	93	2.8	2.5
3	Br_2	1	0–10	90	3.5	1.8
4	Br_2	1.1	−20 to −10	95	3.2	1.1
5	NBS	1	20–30	92	3.4	1.5
6	NBS	1	10–20	91	3.0	2.6
7	NBS	1	0–10	92	1.5	3
8	NBS	1.1	0–10	93	1.7	1.5
9	NBS	1.2	0–10	95	1.8	1.1
10	NBS	1.22	0–10	96	1.8	0.8

[a]HPLC analysis. The conditions for HPLC method were: Thermo scientific-C18 column, C18 (5 μm, 150 mm × 4.6 mm); mobile phase A (0.1% H_3PO_4 in water) and B (CH_3OH); 35:65 A/B→10:90 A/B, 25 minutes, 10:90 A/B, 10 minutes, 10:90 A/B→35:65 A/B, 1 minute, 35:65 A/B, 9 minutes; detection at 210 nm; flow rate = 1.0 mL/min.



Scheme 5 The preparation of diazonium salt and the final desired product **1**.

Table 2 Screening acid system of diazotization[a] and Sandmeyer reaction[b]

Entry	Acid system	Yield (%)
1	Conc. HCl	30
2	Conc. H_3PO_4	25
3	Conc. H_2SO_4	40
4	Conc. HCl/AcOH	35
5	Conc. H_2SO_4/AcOH	46

[a]1.15 equiv. of $NaNO_2$ was used, and the reaction performed at −5 to 5°C, unless otherwise stated.
[b]CuCl/conc. HCl was used.

the reaction would be mess if there were not sufficient diazonium salts formed in the process. As compound **11** was an electron-withdrawing group-substituted aniline, it was difficult to perform salinization thoroughly under the reaction conditions. Therefore, we need to design a route to fully salify **11** to improve the yield of the subsequent diazotization reaction. Considering that **11** was easily soluble in a certain volume of THF, we prepared **11** in THF and introduced hydrogen chloride gas to generate the hydrochloride **17**. Intermediate **17** was poorly soluble in THF and could be collected by centrifugation from the solvent THF without further purification. Intermediate **17** was an ideal intermediate in the manufacturing process because it was chemical stable, free of moisture, and less hygroscopic.

After **17** was obtained, the conditions for the diazotization–Sandmeyer reaction with **17** were further screened and optimized (►**Table 3**). It was found that when the 1.3 equiv.

Table 3 Screening of diazotization[a] and Sandmeyer reaction[b] using 17

Entry	$NaNO_2$ (equiv.)	Yield (%)
1	1.1	85
2	1.2	88
3	1.3	92

[a]The reaction was performed at −5 to 5°C, using conc. HCl as an acid system.
[b]CuCl/conc. HCl was used.

of $NaNO_2$ was used, and the reaction temperature was −5 to 5°C, the final desired product **1** was obtained with the highest yield (92%).

Conclusion

In this article, a novel process for the large-scale production of **1**, a key intermediate of SGLT2 inhibitors, was developed. Using cheap and easily available dimethyl terephthalate (**13**) as the raw starting material, **1** was prepared in six steps, including nitration, hydrolysis, hydrogenation, esterification, bromination, and diazotization. The preparation scale was approximately 70 kg with the total yield of 24%. Compound **11** and its hydrochloride salt **17** are new compounds and chemically stable. Through process screening and optimization, the amount of dibromo impurity **18** produced in the bromination reaction of compound **11** was reduced significantly. The salt-forming reaction of intermediate **11** not only increased the stability of the corresponding compound, but also improved the yield of the subsequent diazotization reaction and Sandmeyer

reaction (from 40 to 92%). This synthetic process is appealing in industry because it starts from cheap and easily available materials, avoids unfriendly oxidative procedure, and harvests high yield and purity of products.

Experimental Section

General

Unless otherwise specified, nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Biospin 400 MHz instrument using tetramethylsilane as the internal standard. All chemical shifts were reported in ppm. Mass spectrometry (MS) spectra were obtained on an Agilent 6460 QQQ mass spectrometer (Agilent, United States) analysis system. All materials were obtained from commercial suppliers and were used without further purification. Reactions' time and purity of the products were monitored by thin-layer chromatography (TLC) on FLUKA silica gel aluminum cards (0.2 mm thickness) with fluorescent indicator 254 nm. Column chromatography was run on silica gel (200–300 mesh) from Qingdao Ocean Chemicals (Qingdao, Shandong, China). Reaction progress and compound purity were determined by high-performance liquid chromatography (HPLC). The conditions of HPLC method were: Thermo scientific-C18 column, C18 (5 µm, 150 mm × 4.6 mm); mobile phase A (0.1% H_3PO_4 in water) and B (CH_3OH), from 35:65 A/B to 10:90 A/B over 25 minutes, and keep 10:90 A/B over 10 minutes, from 10:90 A/B to 35:65 A/B over 1 minutes, and keep 35:65 A/B over 9 minutes; detection at 210 nm; flow rate = 1.0 mL/min.

Dimethyl 2-nitroterephthalate (14)

A dry and clean 1,000 L glass-lined reactor was charged with 98% H_2SO_4 (700 kg) and cooled to 10 to 15°C, and then 97% HNO_3 (85.00 kg, 130.9 mol) was added carefully thereto at temperature not more than 30°C. After the addition, starting material **13** (200.00 kg, 103.0 mol) was added in portions. After the completion of the reaction confirmed by TLC (3:1, PE/EA) sampling, the mixture was added slowly into water (1,200 kg) at temperature not more than 30°C in another 2,000 L glass-lined reactor. The resulting mixture was stirred at 5 to 15°C for 0.5 hour, and the resulting slurry was filtered with a centrifuge and washed with water (600 kg) to give **14** (off-white solid), which was directly used in the next step without further purification.

Sodium 2-nitroterephthalate (15)

A clean 1,000 L glass-lined reactor was charged with water (580 kg) followed by the addition of NaOH (87.00 kg, 217.5 mol). The mixture was stirred until the solid dissolves completely. Then, the entire batch of **14** was added thereto and stirred at 80 to 85°C for 1 hour to give the solution of **15**, which was directly used in the next step.

2-Aminoterephthalic Acid (16)

A clean and nitrogen-purged 1,000 L autoclave reactor was charged with 10% Pd/C (2.50 kg, wetted with ca. 60% water) under nitrogen, and then the solution of **15** was added thereto. After the addition, the reactor was evacuated and purged with N_2 three times, then evacuated and purged with H_2 three times. When the gas replacement was finished, the resulting mixture was purged with H_2 to 0.5 to 1.0 MPa at 80 to 85°C until the end of the reaction. The reaction was cooled to 20 to 25°C, and the reactor was again evacuated and purged with N_2 three times. The resulting reaction mixture was filtered with a titanium rod filter. The filtrate was acidized with AcOH/water (144 kg/400 kg) in another 1,500 L glass-lined reactor. The resulting slurry was filtered with a centrifuge. The filter cake was washed with water (100 kg), dried in a hot air circulation oven at 70 to 75°C until the water content is ≤0.5% to give **16** as a pale solid (179.1 kg, 96% yield from **13** to **16**). ESI-MS (m/z): calcd. for $C_8H_6NO_4^-$ $[M - H]^-$ 180.0375, found: 180.04. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 8 Hz, 1H, ArH), 7.30 (d, J = 4 Hz, 1H, ArH), 7.00 (dd, J = 8, 4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.85, 170.97, 168.75, 150.95, 136.90, 131.64, 117.47, 115.31.

2-Amino-4-(methoxycarbonyl)benzoic Acid (12)

A clean 1,500 L glass-lined reactor was charged with MeOH (480 kg), and then **16** (102.00 kg, 563.1 mol) and TMSCl (90.00 kg, 828.4 mol) were added thereto. After the addition, the reaction was heated to 57 to 63°C and held for 12 hours. When TLC (1:1, PE/EA) indicated the reaction was complete, approximately 320 kg solvent was distilled off under reduced pressure. Water (640 kg) and AcOEt (344 kg) were added thereto and stirred for 0.5 hour. Then, $KHCO_3$ (153.00 kg, 1,528.3 mol) was added carefully and stirred for 0.5 hour. The resulting mixture was filtered with a PP filter. The filtrate was phase-separated in a 1,500 L glass-lined reactor, and the aqueous phase was acidized with AcOH/water (75 kg/128 kg) in another 1,500 L glass-lined reactor. The resulting slurry was filtered with a centrifuge. The filter cake was dried in a hot air circulation oven at 70 to 75°C until the water content is ≤0.5% to give **12** as a brownish-yellow solid (80.2 kg, 73%). ESI-MS (m/z): calcd. for $C_9H_8NO_4^-$ $[M - H]^-$ 194.0532, found: 194.06. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (d, J = 8 Hz, 1H, ArH), 7.41(d, J = 4 Hz, 1H, ArH), 7.03 (dd, J = 8, 4 Hz, 1H, ArH), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.45, 166.48, 151.68, 134.32, 132.11, 117.84, 114.76, 113.42, 52.69.

2-Amino-5-bromo-4-(methoxycarbonyl)benzoic acid hydrochloride (17)

A dry and clean 1,000 L glass-lined reactor was charged with THF (617 kg), and then **12** (87.00 kg, 445.8 mol) was added. The mixture was cooled to 0 to 5°C. Then, NBS (97.59 kg, 548.3 mol) was added in portions thereto at temperature below 10°C. After the addition, the reaction was heated to 25 to 30°C and held for 3 hours. When HPLC indicated the reaction was complete, 470 kg solvent was distilled off under reduced pressure. The residue was solvent-exchanged and concentrated twice with MeCN (137 and 68 kg), and MeCN (87 kg) was added. The resulting mixture was stirred at 57 to 63°C for 0.5 hour, and then cooled to 5 to 10°C for 3 hours. The resulting slurry was filtered with a centrifuge. Another dry and clean 1,000 L glass-lined reactor was charged with THF (430 kg), and then the filter cake was added. Then the mixture was stirred until the solid dissolved. HCl (25 kg) was

bubbled from the bottom of the reactor at temperature below 30°C and stirred for 1 hour. The resulting slurry was filtered with a centrifuge. The filter cake was washed with THF (50 kg), and air-dried to give **17** as a brown solid (96.9 kg, 70%). ESI-MS (*m*/*z*): calcd. for $C_9H_7BrNO_4^-$ [M – H]$^-$ 271.9637, found: 271.95, 273.95. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H, ArH), 7.17 (s, 1H, ArH), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.15, 166.44, 150.50, 136.98, 135.91, 119.14, 113.44, 102.20, 53.08.

5-Bromo-2-chloro-4-(methoxycarbonyl)benzoic Acid (1)

A clean 1,000 L glass-lined reactor was charged with 31% HCl (368 kg), and then **17** (80.00 kg, 257.6 mol) and water (140 kg) were added thereto. Then, the reaction was cooled to −5 to 0°C, and the solution of $NaNO_2$ (23.6 kg, 342.0 mol) in water (140 kg) was added in portions thereto at temperature below 5°C. After the addition, the reaction was cooled to −5 to 5°C and held for 1 hour to give the diazonium salt solution. To another clean 2,000 L glass-lined reactor charged with 31% HCl (436 kg) was added CuCl (28.20 kg) thereto. Then, the diazonium salt solution was added slowly. The resulting mixture was stirred for 1 hour. The resulting slurry was filtered with a centrifuge. The filter cake was washed with water (150 kg), dried in a hot air circulation oven at 70 to 75°C until the water content is ≤0.5% to give **1** as an earth-yellow solid (68.8 kg, 91%). ESI-MS (*m*/*z*): calcd. for $C_9H_5BrClO_4^-$ [M – H]$^-$ 290.9138, found: 290.91, 292.91. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.00 (s, 1H, COOH), 8.09 (s, 1H, ArH), 7.93 (s, 1H, ArH), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.29, 165.00, 136.01, 135.74, 132.80, 131.28, 118.79 (C × 2), 53.54.

2-Amino-3,5-dibromo-4-(methoxycarbonyl)benzoic acid (18, Dibromide Impurity)

2-Amino-4-(methoxycarbonyl)benzoic acid (**16**) (1.95 g, 0.01 mol) was dissolved in THF and stirred for 10 minutes at 0°C, and then NBS (3.56 g, 0.02 mol) was added. The reaction mixture was stirred for 3 hours at room temperature. The reaction solution was concentrated. The residue was purified by column chromatography. ESI-MS (*m*/*z*): calcd. for $C_9H_6Br_2NO_4^-$ [M – H]$^-$ 349.8724, found: 351.9. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H, COOH), 7.97 (s, 1H, ArH), 7.09 (s, 2H, NH), 3.91 (s, 3H).

Supporting Information

Copies of NMR spectra and MS of compounds **12**, **16**, **17**, **1**, and **18** are included in the Supporting Information (►**Figs. S1–14 [online only]**).

Conflict of Interest
We declared no conflict of interest.

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