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Development of Manufacturing Processes for the Carboxylic Acid Key Intermediate of Lusutrombopag: One-pot Reaction Process of Formylation and Horner-Wadsworth-Emmons Reaction

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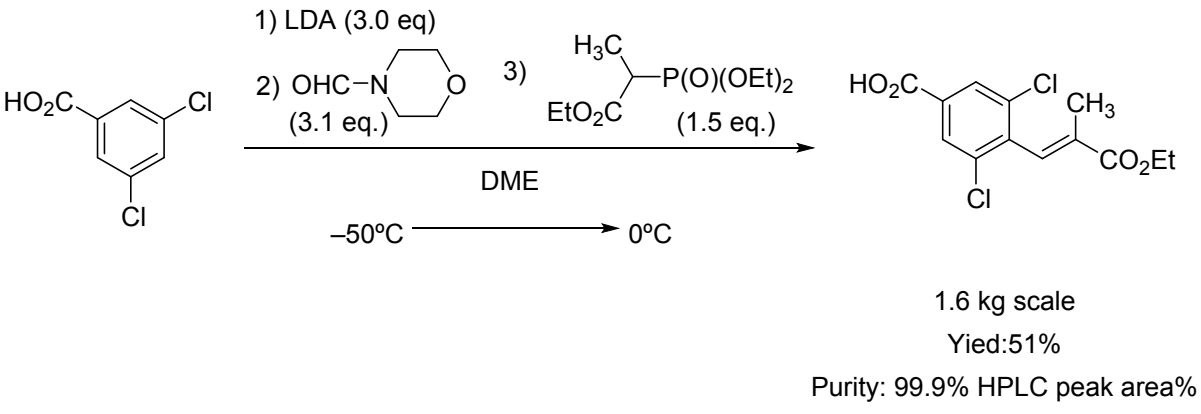
TOC



1.6 kg scale

Yied:51%

Purity: 99.9% HPLC peak area%

ABSTRACT

We describe the development of a one-pot preparation process of (*E*)-3,5-dichloro-4-(3-ethoxy-2-methyl-3-oxoprop-1-en-1-yl)benzoic acid (**3**), which is a key carboxylic acid intermediate of lusutrombopag. This one-pot reaction process is composed of lithiation of 3,5-dichlorobenzoic acid with lithium diisopropylamide (LDA), formylation using *N*-formylmorpholine, followed by olefination employing the Horner-Wadsworth-Emmons reaction with triethyl 2-phosphonopropionate. This method enabled kilogram scale manufacturing of carboxylic acid **3**, a key intermediate of lusutrombopag with high purity, together with a reduced number of steps, improvement of yield, and avoidance of a cumbersome procedure for isolation of the intermediate.

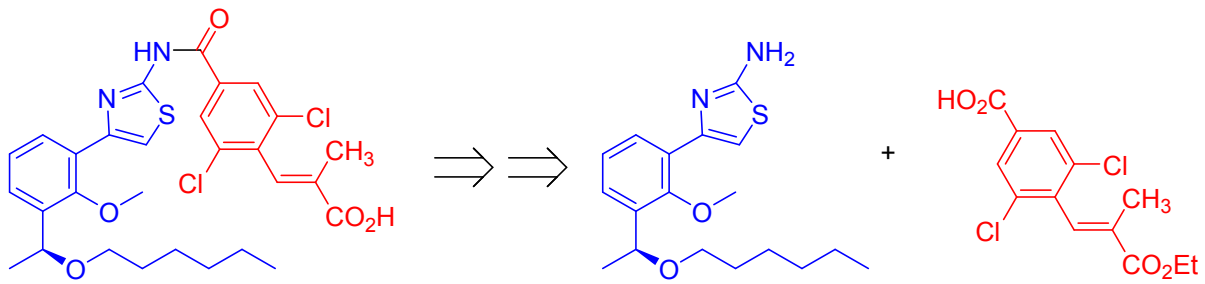
KEYWORDS *one-pot reaction, lithiation, formylation, Horner-Wadsworth-Emmons reaction, lusutrombopag*

INTRODUCTION

Lusutrombopag[1], eltrombopag[2], and avatrombopag[3] are small molecular weight agonists of the thrombopoietin receptor. Among them, lusutrombopag (**1**) is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. It was marketed in 2015 in Japan by Shionogi under the trade name Mulpleta®.

Lusutrombopag has two structural parts, an aminothiazole part and a carboxylic acid part, and is prepared by coupling of an aminothiazole intermediate (**2**) and a carboxylic acid intermediate (**3**) followed by saponification of the ethyl ester moiety (Scheme 1).

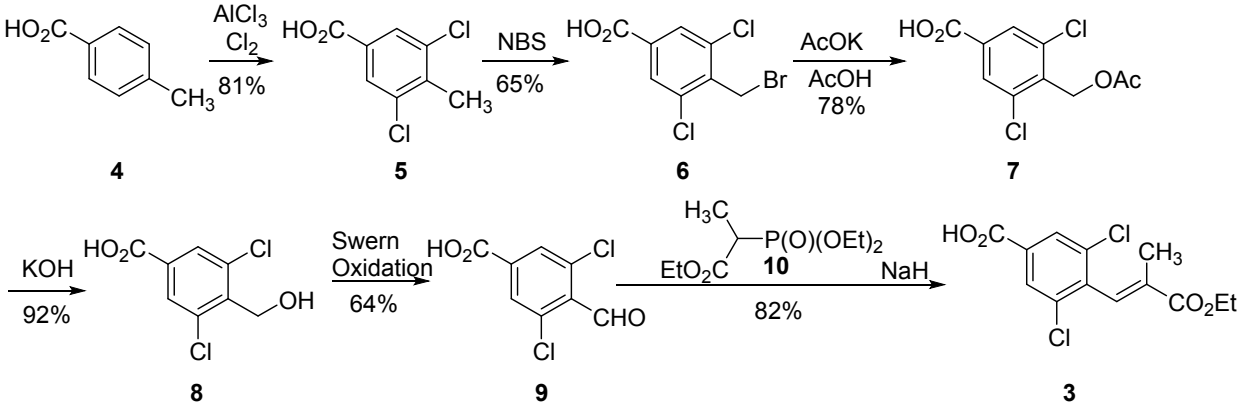
Scheme 1 Retrosynthetic Analysis of Lusutrombopag



Lusutrombopag (1) **2** **3**

In the preliminary manufacturing stage, carboxylic acid **3** was prepared starting from 4-methylbenzoic acid **4** according to the published information[4] as shown in scheme 2. However, it took many synthetic steps (6 steps) to prepare **3** and the overall yield was low (20%). Moreover, mono and tri-chlorinated impurities that formed in the chlorination step were difficult to remove downstream. Additionally, reaction methods which are not applicable for large-scale manufacturing processes were employed, for example, the use of sodium hydride and Swern oxidation.

Scheme 2 Synthesis of 3 according to the published information[4]

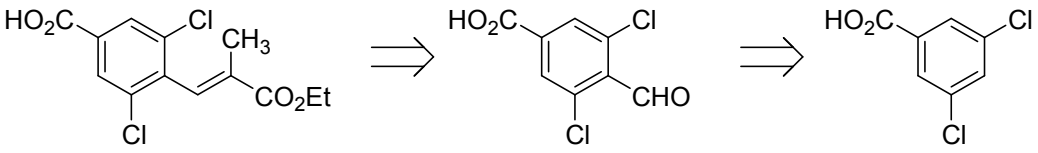


Here we report our attempts to improve the synthetic route and develop manufacturing processes for carboxylic acid **3**, a key intermediate of lusutrombopag.

RESULTS AND DISCUSSION

To solve the issues in the preliminary manufacturing route for the preparation of **3**, we started to investigate a new synthetic route to **9** as shown retrosynthetically in scheme 3. This new synthetic route should reduce the number of synthetic steps, avoid producing the mono and tri-chlorinated byproducts, and make the raw material (compound **11**) readily available. Also, by examining the reaction conditions of the Horner-Wadsworth-Emmons reaction, we were targeting to develop a more practical synthetic method for **3**.

Scheme 3 Retrosynthetic Pathway of Improved Synthetic Method for Carboxylic Acid 3



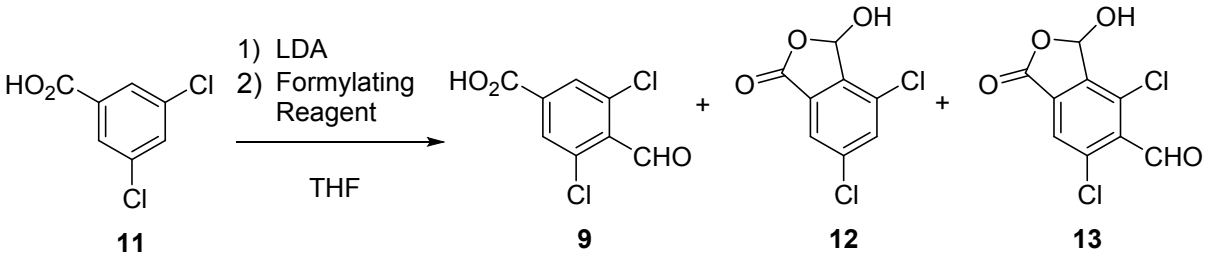
3 **9** **11**

First, the formylation of **11** was investigated (Table 1). It was found that the leaving group of the formylating agents had an impact on the easiness of stirring of the reaction mixture. When *N, N*-dimethylformamide was used as the formylating reagent, the reaction slurry had low fluidity and was difficult to stir, making this reagent unsuitable for

large-scale manufacturing. The fluidity of the slurry in *N,N*-dibutylformamide was better than that in case of DMF, but *N,N*-dibutylformamide decreased the reactivity (entry 2). When *N*-formylmorpholine[5] was used as the formylating reagent (entry 3), the fluidity of the reaction slurry was superior to that of using *N,N*-dimethylformamide.

Lithiation of **11** by LDA followed by treatment with the formylating reagent gave the desired aldehyde **9** along with the undesired formylated isomers **12** and **13**. To improve the selectivity, the effect of temperature was examined, showing that the selectivity was improved at lower reaction temperature (entries 4-6). We speculated that lithiation of the 4-position of compound **11** was controlled kinetically and that lithiation of the 2-position of compound **11** was controlled thermodynamically.

Table 1 Effect of the formylating reagent in a 2-step manufacturing method



11 **9** **12** **13**

entry	formylating reagent	equiv.	temperature (°C)	ratio of compounds (%) **9**:**11**:**12**:**13**[a]

1	*N*,*N*-dimethylformamide	2.5	−50	64:10:24:2
2	*N*,*N*-dibutylformamide	2.5	−50	53:32:15:-
3	*N*-formylmorpholine	2.5	−50	64:8:23:5
4	*N*-formylmorpholine	5.0	−20	45:17:33:5
5	*N*-formylmorpholine	5.0	−50	65:9:22:4
6	*N*-formylmorpholine	5.0	−80	73:6:17:4

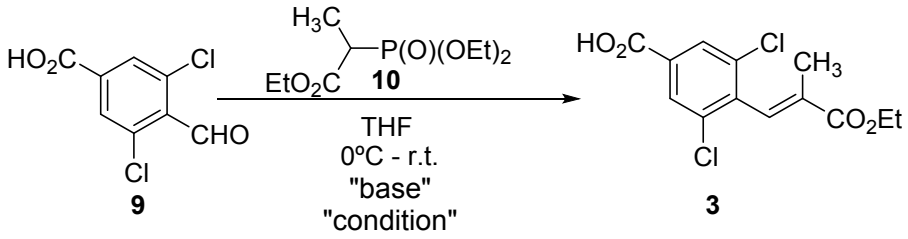
[a]Ratio in reaction mixture was determined by ^{1}H-NMR

We next examined the bases used in the Horner-Wadsworth-Emmons[6] reaction (Table 2). Sodium hydride used in the preliminary manufacturing route gave a good yield (entry 1), but it is not applicable for large-scale production due to safety concerns.

When a weak base (entries 2-4) was used, the enolate of triethyl 2-phosphonopropionate was not generated, and when DBU was used, the yield of the desired **3** was low, presumably due to insufficient enolate formation (entry 5). Using a strong base, *t*-BuOK, greatly improved the yield of **3** and the reaction rate (entry 6). A less basic base was explored, and lithium hydroxide was found to be effective (entry 7). Lithium hydroxide, somewhat less basic than *t*-BuOK, was considered to have appropriate basicity for this reaction. Furthermore, isolation of compound **3** from the

reaction mixture with lithium hydroxide is easier than with *t*-BuOK because *t*-BuOH produced in working-up disturbed extraction in the case of *t*-BuOK.

Table 2 Horner-Wadsworth-Emmons reaction of 9



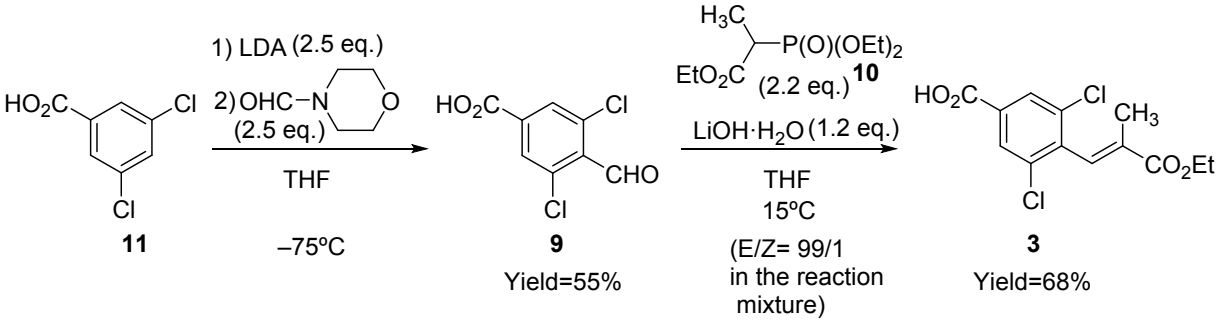
entry	base (equiv.)	time (h)	HPLC peak area% of **3**
1	NaH (2.2)	0.25	>95%
2	Et_3N (2.0)	-	no reaction[a]
3	Cs_2CO_3 (2.0)	-	no reaction
4	K_2CO_3 (2.0)	-	no reaction
5	DBU (2.0)	5	15 %
6	*t*-BuOK (2.2)	0.25	>95%
7	$LiOH{\cdot}H_2O$ (2.2)	2.7	>95%[b]

[a]Carried out at 40°C 1.5 h and 70°C 2 h. [b]Quantitative yield determined by HPLC

Based on our findings, we established a scalable 2-step manufacturing method of **3**, giving 35 kilograms of **3** in an overall yield of 38% (Scheme 4). As mentioned in table 1,

the laboratory Step 1 experiment which was carried out at −80°C gave the high selectivity of compound **9**, but the manufacturing was carried out at -75°C owing to the ability of the apparatus.

Scheme 4 The 2-step manufacturing method for 3



Some issues remained with this 2-step manufacturing method. The procedure for isolation of **9** (four extractions and five concentrations) was cumbersome, and the specification setting of **9** was very difficult as there was no good derivatization method for the analytical method validation. The reason why derivatization method was necessary was that the peak of compound **3** was very broad. Moreover, product **3** was prone to be hydrolyzed to the corresponding dicarboxylic acid due to the water contained in lithium hydroxide hydrate, and the dicarboxylic acid led to fatal impurity in

the downstream steps. Furthermore, the reaction had to be carried out at higher temperatures (around -50°C) owing to a change of the apparatus.

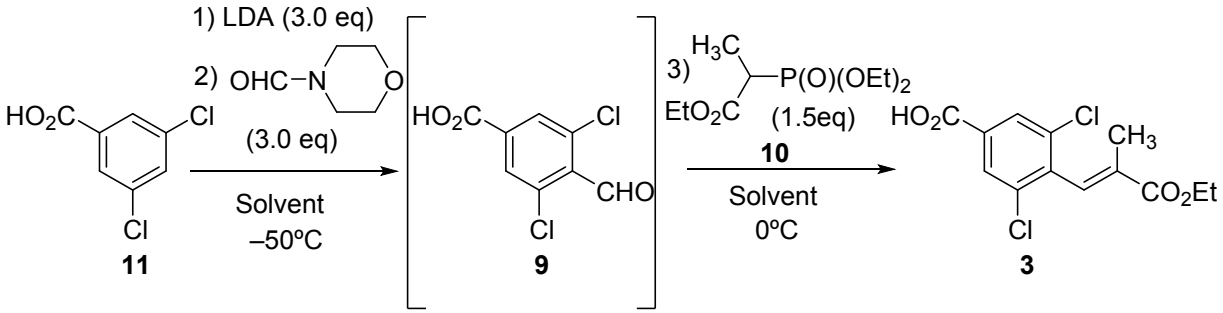
We therefore tried to further improve this 2-step manufacturing method and focused on investigation of a one-pot reaction process[7-9], which did not require isolation of **9** and could be carried out under anhydrous condition ($LiOH \cdot H_2O$ not used as a base).

We first examined the solvent for the one-pot method (Table 3). The selectivity of compound **9** in the reaction mixture after formylation in tetrahydrofuran (THF) used in the above-mentioned 2-step manufacturing method was almost as same as that of Table 1. The selectivity of 1,2-dimethoxyethane (DME) at −50°C was much better than that of THF at −80°C and the was highest selectivity in the five solvent.

THF gave **3** in 67% yield in the one-pot method (entry 1). Cyclopentylmethyl-ether (CPME) and diglyme gave **3** in somewhat lower yield (42% and 40% respectively, entries 2, 3). The decreased yield was presumably due to lump formation in the reaction mixture. However, when methyl *t*-butyl ether (MTBE) and DME were used, the yield of **3** was improved to 70% and 79%, respectively (entries 4, 5). Moreover, the ratio of the *E*-form and the *Z*-form of **3** in DME was slightly better than with THF and

MTBE. Comprehensively evaluating, DME is the most suitable solvent for one-pot reaction.

Table 3 Effect of the solvent in one-pot reaction



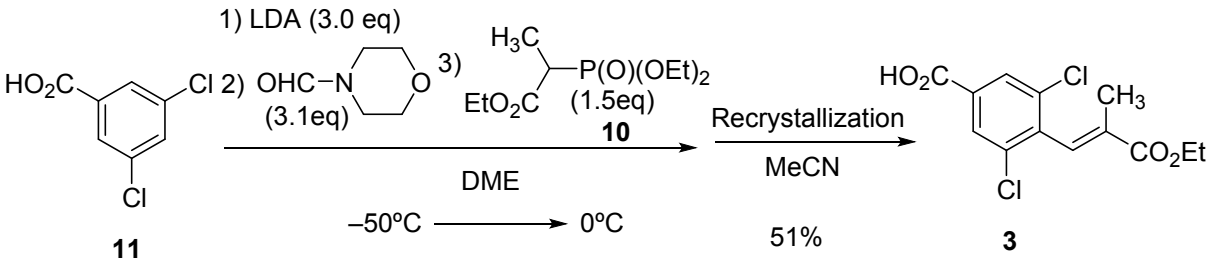
entry	solvent	ratio of compounds (%) **9**:**11**:**12**:**13**[a]	yield (**3**) (%)[b]	*E*/*Z*[c]
1	THF	71:5:18:6	67	94/6
2	CPME	72:16:9:3	42	86/14
3	Diglyme	83:9:3:5	40	98/2
4	MTBE	65:21:11:3	70	94/6
5	DME	84:4:4:8	79	98/2

[a]Ratio in reaction mixture was determined by ^{1}H-NMR. [b]Yields were determined by HPLC analysis using an authentic sample. [c]*E*/*Z* were determined by HPLC analysis. RRT (Relative retention time) of *Z* isomer is 0.93, which was calculated based on the retention time of *E* isomer

We next examined crystallization solvent in the final isolation step of **3**. In the 2-step manufacturing method, ethyl acetate-heptane was employed as a crystallization solvent of **3**, but a considerable amount of **3** was lost in the mother liquor (10%). The solubility of **3** in some solvents was investigated. Among the solvents investigated (1,2-dimethoxyethane, 2-propanol, ethyl acetate and acetonitrile, toluene, acetone, etc.), acetonitrile was found to have the balance of solubility and polarity to remove impurities, and was considered to be a suitable recrystallization solvent.

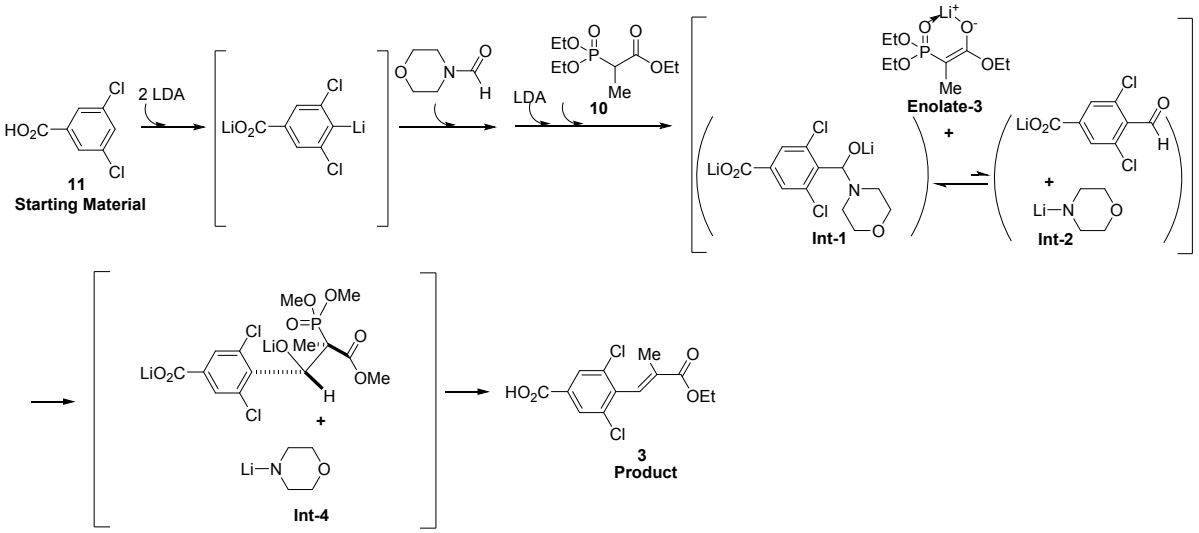
The above-mentioned examination of the reaction and recrystallization solvents led to the establishment of a one-pot reaction method, and **3** was obtained in 51% yield at 1.6 kg scale with a purity of 99.9 HPLC peak area% (Scheme 5). Yield of compound **3** in reaction mixture was 79% as above-mentioned and total loss of aqueous layer, mother liquid and wash liquid was 28%

Scheme 5 One-pot preparation method of 3 from 11



The established one-pot reaction process is speculated to proceed according to the following mechanism (Scheme 6). Reaction of compound **11**, *N*-formylmorpholine and triethyl 2-phosphono-propionate **10** with three equivalents of LDA gives a mixture of enolate of phosphonate (Enolate-3) and a formylated adduct, which is in an equilibrium between Int-1 and Int-2. Int-2, which exists in a small amount in the equilibrium, reacts with Enolate-3 to generate the adduct (Int-4) which leads to the desired aldehyde **3**. Product **3** (*E*-form) seems to be preferred, because steric hindrance between methoxy carbonyl and hydrogen atom (Int-4) is smaller than that between the methoxy carbonyl and aryl group.

Scheme 6 Mechanism of the one-pot reaction



CONCLUSION

In conclusion, we have developed a one-pot manufacturing method for the lusutrombopag key intermediate **3** from readily available carboxylic acid **11**. This one-pot reaction process is composed of lithiation of **11**, formylation with *N*-formylmorpholine and the Horner-Wadsworth- Emmons reaction[10]. The synthetic method enabled kilogram scale manufacturing of **3** in high yield along with high purity, together with reduction in the number of steps, improvement of yield, and avoidance of cumbersome procedures for isolation of the intermediate.

Experimental Section

All experiments were run under a nitrogen atmosphere. Solvents and reagents were obtained from commercial sources and used without further purification. High performance liquid chromatographic (HPLC) analysis was carried out using Shimadzu LC-10ADVP or Shimadzu LC-2010. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz Varian FT spectrometer or a Bruker Avance III HD 400 MHz or Varian Unity Inova-500. LCMS were recorded on a Shimadzu LCMS-2010EV. DSC (Differential Scanning Calorimeter) were recorded on Perkin Elmer Pyris 1.

HPLC Method for analysis of 3

Column: Unison UK-C18, 4.6 × 100 mm, 3 µm (Imtakt)

Mobile phase A: 0.1% CF_3COOH in purified water. Mobile phase B:CH_3CN.

B concentration (Gradient): 0-2 min 35%, 2-20 min 35-60%, 20-30 min 60%, 30-30.1 min

60-35%, 30.1-45 min 35%.

Flow rate: 1.0 mL/min

Injection volume: 10 µL

Column temperature: 35°C

Wavelength: 254 nm

Sample was diluted with CH_3CN/H_2O (40/60 (v/v))

2-step manufacturing method

3, 5-dichloro-4-formylbenzoic acid (9)

To a solution of 3,5-dichlorobenzoic acid (**11**) (70.0 kg, 366 mol) in tetrahydrofuran (504.0 kg) under nitrogen, a solution of 26% lithium diisopropylamide (LDA) in tetrahydrofuran-heptane-ethylbenzene (377.1 kg, 98.1 kg as LDA, 915 mol) was added at −75°C for 3 h. The reaction mixture was stirred at the same temperature for 30 min. To the mixture was added *N*-formylmorpholine (105.5 kg, 916 mol) in tetrahydrofuran (129.5kg) for 2 h. The resulting mixture was stirred at the same temperature for 2 h. Water (196 L) was added to the reaction mixture and it was stirred for 30 min. The reaction mixture was added below 10°C to the solution of water (301 L) and 62.5% sulfuric acid (189.0 kg) for 30 min. The line was washed with the solution of water (63 L) and tetrahydrofuran (35.0 kg). The organic layer was separated and washed with

water (244 L x 3). The combined aqueous layer was extracted with ethyl acetate (194 L). The organic layers were combined and was concentrated under reduced pressure to 210 L. To the residue was added ethyl acetate (210 L), and it was concentrated to the volume of 210 L (repeated four times). The residue was adjusted to the volume (210 L) with ethyl acetate, and the mixture was stirred at 45°C for 10 min and then cooled to 22°C. To the solution was added for 70 min heptane (144.2 kg) and the reaction mixture was stirred for 10 min at the same temperature, then cooled to 5°C and stirred for 3.5 h. The precipitated solid was filtrated, washed with a mixture of ethyl acetate-heptane (35 L-24.2 kg) below 10°C, and dried to obtain **9** as a solid (44.2 kg, 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.4 (1H, s), 7.96 (2H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.46, 164.32, 135.87, 134.97, 133.60, 129.91. MS (ESI$^-$) m/z 217 [M-H]$^-$. Decomposition point: 160°C (Measured by DCS).

4,6-dichloro-3-hydroxy-2-benzofuran-1(3H)-one (12)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (1H, d, J = 4.0 Hz), 7.67 (1H, d, J = 4.0 Hz), 6.68 (1H, s) . ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.55, 141.48, 138.27, 134.94, 131.27, 130.29, 124.05, 96.79. MS (ESI$^-$) m/z 217 [M-H]$^-$.

4,6-dichloro-3-hydroxy-1-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde (13)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (1H, s), 7.88 (1H, s), 6.73 (1H, s), ^{13}C NMR (100 MHz, $CDCl_3$) δ187.73, 165.26, 142.94, 139.59, 135.56, 132.38, 131.67, 126.05, 96.45. MS (ESI^-) m/z 260 $[M-H]^-$ (The sample was derivatized with NH_2OH·HCl aqueous solution. CH=O → CH=NOH))

3,5-dichloro-4-[(1*E*)-3-ethoxy-2-methyl-3-oxoprop-1-en-1-yl]benzoic acid (3)

To a suspension of lithium hydroxide monohydrate (18.6 kg, 443 mol) in tetrahydrofuran (50.8 kg) under nitrogen, a solution of **9** (44.2 kg, 202 mmol) in tetrahydrofuran (97.2 kg) was added at 0°C for 1 h. To the mixture was added triethyl 2-phosphonopropionate (**10**) (57.7 kg, 242 mol) in tetrahydrofuran (54.4 kg) for 1.5 h maintaining the temperature below 15°C. The resulting solution was stirred at 15°C for 2 h. To the solution were added a solution of 62.5% sulfuric acid (33.2 kg) and water (184 L) for 1 h. After the organic layer was separated, to the organic layer were added ethyl acetate (221 L) and water (88 L). The organic layer was separated and washed successively with water (88 L) and the solution of sodium chloride (19.9 kg) and water (88 L). The organic layer was separated and concentrated to less than 132 L under

reduced pressure. Ethyl acetate (442 L) was added to the residue and concentrated to less than 132 L, and the same operation was repeated. The residue was heated to 45°C, a suspension of activated carbon (1.3 kg) and ethyl acetate (7 L) was added, and the mixture was stirred for 30 min. The mixture was filtrated, and the activated carbon was washed with ethyl acetate (133 L) twice. The filtrate was concentrated to less than 132 L, and the residue was heated to 45°C and stirred at the same temperature for 10 min. After cooled to 23°C, n-heptane (91.1 kg) was added at the same temperature and then stirred for 10 min. After cooling below 5°C, the mixture was stirred for 1 h. The precipitated crystals were filtrated, washed by ethyl acetate (44 L), and dried to obtain **3** as a crude solid (50.6 kg, yield:83%).

Recrystallization: To the obtained crude solid of **3** (40.0 kg) was added ethyl acetate (108.0 kg) and the mixture was heated to 75°C and stirred for 30 min. After dissolution, the solution was cooled to 60°C and stirred for 30 min, stirred at 30°C for 1 h, and to 0°C for 1 h. Crystals precipitated were filtrated, washed by ethyl acetate (36 kg), and dried to obtain **3** (32.9 kg, recrystallization yield: 82%, overall yield: 68 %, 99.9 HPLC peak area%).

One-pot reaction

3,5-dichloro-4-[(1*E*)-3-ethoxy-2-methyl-3-oxoprop-1-en-1-yl]benzoic acid (3)

To a solution of **11** (2.00 kg, 10.5 mol) in 1,2-dimethoxyethane (28.0 kg), a solution of 25% LDA in tetrahydrofuran-heptane-ethylbenzene (13.20 kg, 30.8 mol) was added at −55°C for 1 h under nitrogen atmosphere and the reaction mixture was stirred at that temperature for 30 min. To the mixture was added *N*-formylmorpholine (3.74 kg, 32.5 mol) in 1,2-dimethoxyethane (3.0 kg) at −55°C for 40 min and the resulting mixture was stirred for 1 h. To the reaction mixture was added triethyl 2-phosphonopropionate (**10**) (3.74 kg, 15.7 mol) in 1,2-dimethoxyethane (3.0 kg) at 0°C for 45 min and the resulting solution was stirred for 2 h. To the solution were added 35% sulfuric acid (15.8 kg) for 40 min and water (16.0 kg). The organic layer was separated and washed with water (8.0 kg) and concentrated under reduced pressure. Acetonitrile (16.0 kg) was added to the residue and the resulting suspension was stirred at 25°C for 1 h, and stirred at 0°C for 5.5 h. The precipitated crystals were filtrated and washed with acetonitrile (3.2 kg) at 5°C. The obtained crystals were dissolved at 75°C in acetonitrile (16.0 kg) and the

solution was cooled to 60°C and stirred for 30 min. The suspension was cooled to 30°C for 1 h and stirred for 45 min, and then cooled to 5°C for 40 min and stirred for 3 h. The precipitated crystals were filtrated and washed by acetonitrile (3.2 kg) at 5°C. The obtained crystals were dissolved at 75°C in acetonitrile (13.0kg) and the solution was cooled to 60°C and stirred for 30 min, cooled to 30°C for 1 h and stirred for 70 min, and cooled to 5°C for 30 min and stirred for 4 h. The precipitated crystals were filtrated, washed with acetonitrile (3.2 kg) at 5°C, and dried to obtain **3** (1.63 kg, 51%, 99.9 HPLC peak area%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.7 (1H, br), 7.97 (2H, s), 7.41 (1H, d, J = 1.2 Hz), 4.25 (2H, q, J = 7.1 Hz), 1.70 (3H, d, J = 1.2 Hz), 1.30 (3H, t, J = 7.1 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.06, 164.72, 137.11, 133.65, 133.53, 133.01, 132.56, 128.52, 60.97, 14.30, 13.99. MS (ESI$^-$) m/z 301 [M-H]$^-$.

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Notes

The authors declare no competing financial interest.

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