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Development of a Practical and Scalable Synthesis of a Potent CRTH2 Antagonist

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ABSTRACT: This contribution describes the process research and development of a practical and scalable synthetic method towards compound **1**, which has a potent CRTH2 antagonistic activity. The medicinal chemistry synthetic route and second generation synthetic route had several issues in scale-up synthesis. In contrast, the synthetic method described here does not require purification by column chromatography for all steps, and the formation of impurities is suppressed well. This highly efficient and scalable process was successfully demonstrated in the large-scale synthesis of **1**.

INTRODUCTION

4-{3-[3-(3-Benzhydryl-6-oxo-1,6-dihydropyridazin-1-yl)-propyl]phenoxy}butanoic acid (**1**, Figure 1) has potent

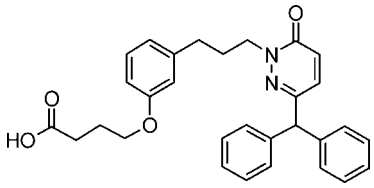

Figure 1. Structure of compound **1**.

CRTH2 antagonistic activity. CRTH2 is expressed on inflammatory cells, such as Th2 cells, eosinophils, and basophils, and induces the chemotaxis of these cells. CRTH2 also plays important roles in cytokine release by Th2 cells and in the degranulation of eosinophils. CRTH2 antagonists are expected to be useful as anti-inflammatory agents in the treatment of patients with allergic diseases.[1] The medicinal chemistry synthetic method for compound **1** had several disadvantageous issues with regard to scale-up synthesis (Scheme 1). Further, the second-generation synthetic method constructed via aldol reaction with a base (Scheme 2) included a poorly reproducible reaction that should be avoided in scale-up synthesis. Under such circumstances, we were required to synthesize 30 kg of **1**. This article describes our efforts to develop an efficient synthetic method for the first GMP delivery of **1** which is capable of being operated on a scale-up synthesis level.

RESULTS AND DISCUSSION

The medicinal chemistry synthetic method is shown in Scheme 1. This method was associated with several drawbacks, as summarized below.

- Many steps (step c, f, g, h, and j) required SiO_2 column chromatography.
- Yield of compound **10**[2] was low (typically 33%).
- Preparation of iodide **7** via mesylate **6** was undesirable from the point of view of efficiency; rather, direct alkylation using mesylate **6** with pyridazinone **11** would be a more efficient strategy.

Second-Generation Synthetic Method (400-g-Scale Synthesis). We were urgently required to prepare 400 g of final product **1** for preclinical study. To address these issues with the medicinal chemistry synthetic method, we focused on the preparation of **10** and **12** (Scheme 2). First, we attempted to synthesize **10** using the aldol reaction with a base. The combination of LDA and ethyl glyoxylate (**9**) worked well, and the desired **10** was obtained. After treatment with hydrazine hydrate, pyridazinone **11** was prepared in a typically 65% yield. For the *N*-alkylation step, the exchange of mesylate **6** to iodide **7** was avoided; rather, direct alkylation was accomplished using LiH as a base, and the desired product **12** was prepared. Finally, we were able to prepare 435 g of **1** for preclinical study. However, a number of issues were identified during the preparation of this sample that required improvement for delivery of a 30-kg campaign, as listed below.

- SiO_2 column chromatography was necessary in step b.
- Low reproducibility of the aldol reaction might be a significant issue for large-scale synthesis.
- Low yield at the pyridazinone ring formation step.
- Use of LiH in the *N*-alkylation step might be unfavorable from the point of view of safety.
- In the final recrystallization step, loss of final product **1** to the filtrate should be prevented (approximately 25%).

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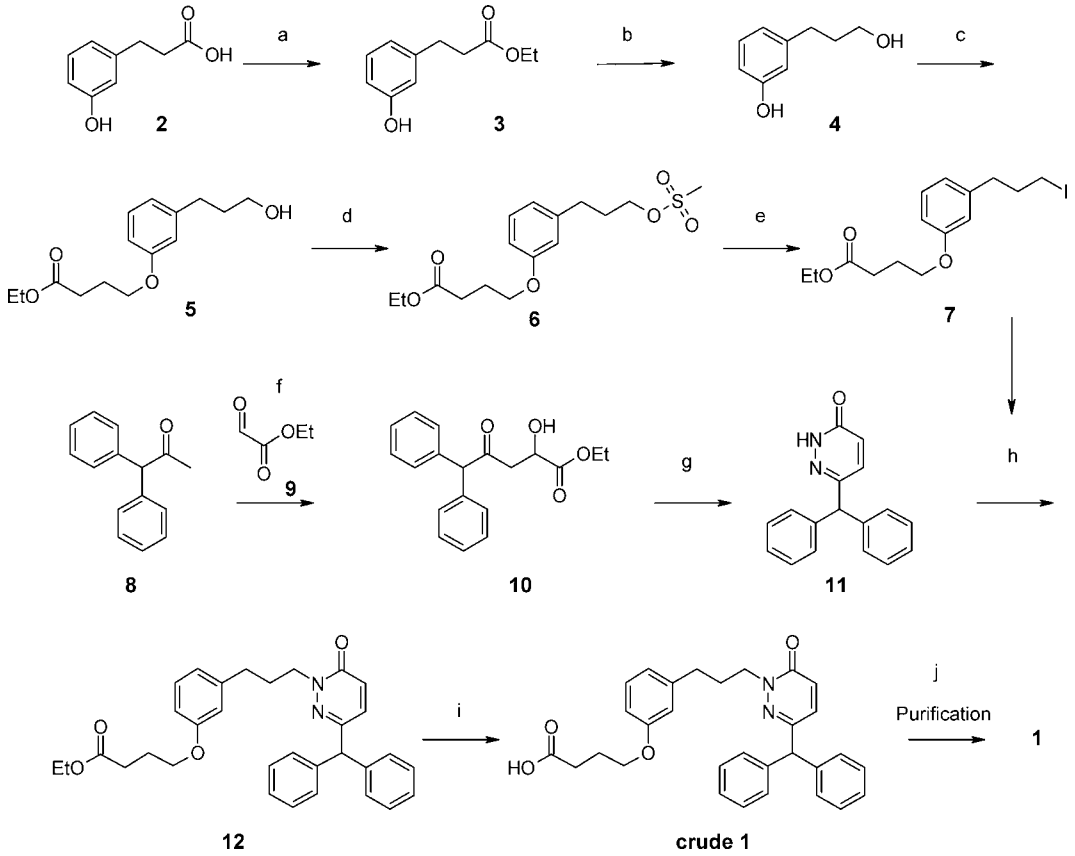
Scheme 1. Medicinal chemistry synthetic method (first-generation method)[a]



[a]Reagents and conditions: (a) H_2SO_4 (cat.), EtOH, reflux, 24 h, quantitative yield, (b) DIBAL (3.3 equiv), CH_2Cl_2, 5 °C, 1 h, 94% yield, (c) K_2CO_3 (2.6 equiv), ethyl 4-bromobutyrate (1.2 equiv), DMF, 60 °C, 10 h, SiO_2 column chromatography, 81% yield, (d) MsCl (1.3 equiv), Et_3N (1.8 equiv), CH_2Cl_2, 5 °C, 1 h, quantitative yield, (e) NaI (4 equiv.), acetone, 25 °C, 12 h, 96% yield, (f) **9** (1 equiv), neat, 135 °C, 1 day, SiO_2 column chromatography, 33% yield, (g) hydrazine hydrate (1 equiv), MeOH, 130 °C, 1 day, SiO_2 column chromatography, 77% yield, (h) LiH (3 equiv), DMF, 25 °C, 4 h, SiO_2 column chromatography, 91% yield, (i) aq NaOH, MeOH, 25 °C, 12 h, then aq HCl, 94% yield, (j) SiO_2 column chromatography, CH_2Cl_2–MeOH, 73% yield.

New Approach for 30-kg-Scale Synthesis (Third Generation). Under such circumstances, there was strong demand for the development of a suitable production process for **1** with higher overall yield that does not require SiO_2 column chromatography purification. Our efforts were focused on designing a safe, scalable, efficient, and reproducible synthesis of **1** that incorporates the following key points: (1) aldol reaction, (2) pyridazinone ring formation, and (3) recrystallization conditions. During this research, 3-(3-hydroxypropyl)phenol (compound **4**) could be purchased as a commercially available compound. We investigated a new strategic approach to the 30-kg synthesis campaign of **1**, which we describe and discuss below.

Optimization for Aldol Reaction.[3] Aldol reaction was attempted under various conditions (Table 1).

As shown in Table 1, LDA gave the best results in comparison with those with other bases such as TMP–*n*-BuLi (entry 6), and LHMDS (entry 7). The use of sodium hexamethyldisilazane (NaHMDS) did not give the desired compound (entry 8). Further, no significant difference was observed between −78 °C and −65 °C (entries 1 and 2). In the second-generation synthesis, the aldol reaction was not reproducible. To solve this issue for scale-up synthesis, we focused on the reaction temperature for enolization (Figure 2). As expected, a lower-temperature reaction gave better results than one at a higher temperature. When the reaction was conducted at less than −60 °C, the formation of impurity A was suppressed until it represented an area of less than 5%. This means that a higher temperature increased the equilibrium of tertiary enolate B because of thermodynamic stability and also gave impurity A (Scheme 3).

To optimize reaction conditions, the effect of an equivalent of ethyl glyoxylate (**9**) was investigated. Results showed that the best yield was obtained with the use of 2.0 equiv of **9**. Further, solvent screening was done using THF, CPME, and toluene (Table 1, entries 3 and 4). THF was selected because it gave the best reaction profile on HPLC. In the next stage, the stability of **10** during the quenching and concentration processes was investigated. During quenching with an aqueous acid such as HCl, the ratio of product **10** was gradually decreased, and the formation of impurity B was observed. In spite of the maintenance of neutral conditions, the product was progressively decomposed, and the formation of impurity C was observed (Figure 3). Further, compound **10** was degraded during storage at 5 °C. These factors may have been significant in large-scale synthesis

Pyridazinone Ring Formation.[4] Owing to the instability of compound **10**, a one-pot reaction with hydrazine hydrate was attempted as shown Figure 4. During the reaction, dihydropyridazinone intermediate A was observed at around −10 °C on

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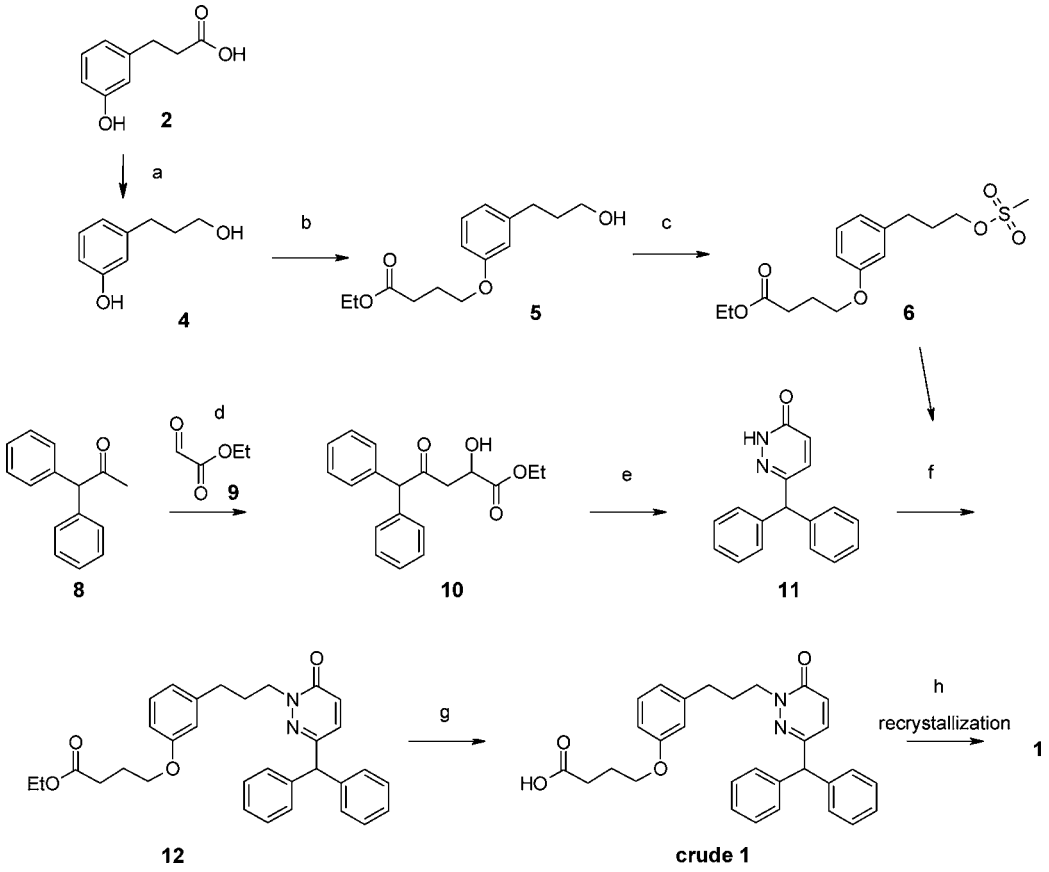
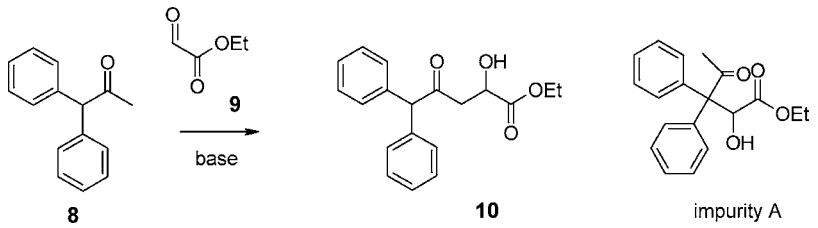
Scheme 2. Second generation synthetic method (400-Gram-Scale Synthesis)[a]



[a]Reagents and conditions: (a) Red-Al (5.5 equiv), toluene, THF, 70 °C, 2 h, (b) K_2CO_3 (3.0 equiv), ethyl 4-bromobutyrate (1.1 equiv), DMF, 80 °C, 3 h, SiO_2 column chromatography, 78% yield in 2 steps, (c) MsCl (1.3 equiv), Et_3N (1.8 equiv), toluene, 25 °C, 1 h, 95% yield, (d) LDA (1.5 equiv), THF, −60 °C then **9** (2.1 equiv, polymer in toluene), −60 °C, 1.5 h, (e) hydrazine hydrate (4.3 equiv), EtOH, toluene, 140 °C, 65% yield in 2 steps, (f) LiH (3 equiv.), DMF, 25 °C, (g) aq NaOH, MeOH, 50 °C, 2 h, then aq HCl, 85% yield in 2 steps, (h) recrystallization with EtOAc, 73% yield, loss to the filtrate; 25%.

Table 1. Base and solvent screening for aldol reaction



entry	base (equiv)/solvent	HPLC area %[e] 10	8	impurity A	comments
1[a]	LDA[c] (1.1)/THF	70	13	4	–
2[b]	LDA[c] (1.1)/THF	70	14	3	–
3[a]	LDA[c] (1.5)/THF	69	12	7	–
4[a]	LDA[c] (1.5)/CPME	45	40	5	–
5[a]	LDA[c] (1.5)/toluene	57	13	15	–
6[a]	TMP[d]–*n*-BuLi (1.1)/THF	65	22	5	–
7[a]	LHMDS (1.1)/THF	64	13	11	–
8[a]	NaHMDS (1.1)/THF	–	–	40	messy

[a]Reaction temperature −65 °C. [b]Reaction temperature −78 °C. [c]LDA was prepared in situ between *n*-BuLi and diisopropylamine in THF. [d]2,2,6,6-Tetramethylpiperidine. [e]Determined by HPLC method A (see Experimental Section).

LC−MS analysis. However, the following dehydration reaction did not complete at this temperature but was accelerated by warming of the reaction mixture to around 40 °C. The yield of desired pyridazinone **11** was typically 60%, which was unsatisfactory. During this stage of optimization for scale-up synthesis, the hydrazone intermediate B was observed in the

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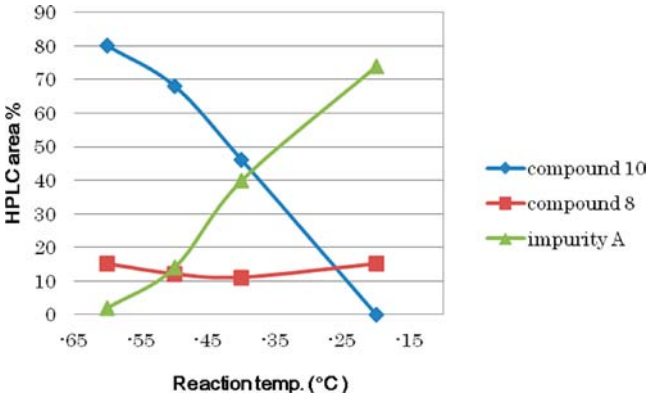


Figure 2. Effect of reaction temperature.

aqueous layer that was produced after quenching. It was possible that the hydrazone intermediate B might be hydrolyzed to the desired pyridazinone **11** (Figure 4).[5] As expected, intermediate B was converted to the desired pyridazinone **11** during heating at 70 °C for 24 h. Finally, the pyridazinone **11** was obtained in 76% yield, which was an increase of 11% over that with the second-generation synthetic method. This highly reproducible process was demonstrated in a large scale, and 26.3 kg of **11** was prepared.

Synthesis of ***Crude 1****.* In the second-generation synthetic method, the compound **5** was purified with SiO_2 column chromatography. Here, however, one-pot synthesis of ester compound **12** was attempted via mesylate. In the *N*-alkylation step, the first- and second-generation methods used LiH as a base. To avoid the use of LiH, various bases were screened, including K_2CO_3, *t*-BuOK, EtONa, KOH, and NaOH (Table 2).[6] From the results, NaOH in EtOH was selected as a reaction condition that gave the best reaction profile. In the second-generation synthetic method, extraction with a large amount of toluene was necessary to recover the desired **12** from the reaction mixture. In contrast, following the improvement of *N*-alkylation conditions, we had the chance to conduct a one-pot hydrolysis reaction. As expected, subsequent hydrolysis was performed by the addition of aqueous NaOH to the *N*-alkylation reaction mixture. After acid treatment and phase separation, the desired **crude 1** was isolated as crystals with *n*-heptane−EtOAc in good yield (typically 54−57% in four reactions) (see Scheme 4). This crystallization method was optimum, providing an increase in purity on HPLC from 86%

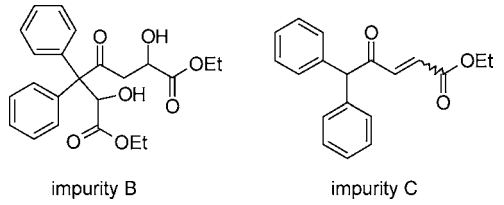


Figure 3. Structures of impurity B and C.

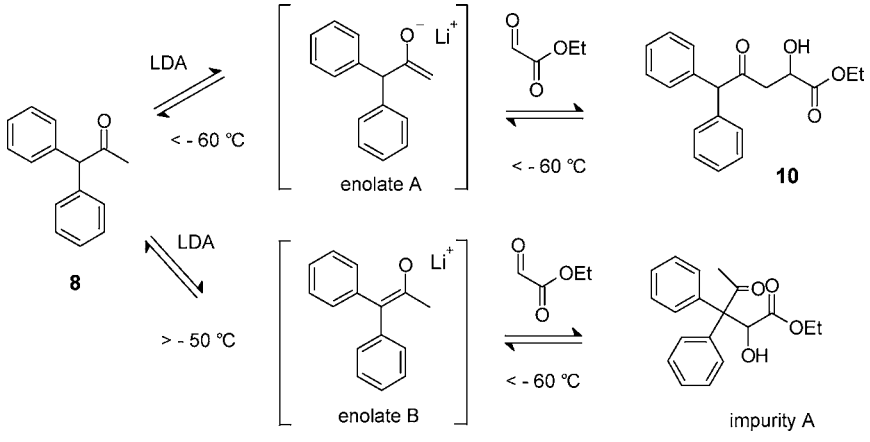
to 97% without loss to the filtrate. This highly efficient process was successfully demonstrated in large-scale synthesis, and 32.7 kg of **crude 1** was prepared.

Recrystallization Step. To improve loss to the filtrate and increase the purity of **crude 1** to meet our desired purity (>99%), recrystallization conditions were studied. Most low polar impurities that were detected back on HPLC analysis (HPLC method A) in comparison with **1** were removed to the filtrate during crystallization in the preceding step. We were therefore required to remove the highly polar impurities which were detected forward of **1** on HPLC analysis. We therefore focused on the aqueous conditions as solvents. The conditions of aqueous EtOH, aqueous *i*-PrOH, and aqueous acetone were tested for the recrystallization step (Table 3). From these results, aqueous *i*-PrOH was selected in consideration of refining efficiency (entry 1). Further, to avoid amorphous contamination, the crystallization process was accomplished as shown in Figure 5. Important factors in this procedure were timing of the addition of water and addition of seed crystals. Using this newly developed synthetic method, 30.6 kg of **1** was synthesized with a purity of 99.7% in 94.2% yield (Table 4). Loss to the filtrate was only 1.8%. The procedure is described in detail in the Experimental Section.

■ CONCLUSION

A practical and scalable synthetic method of **1** was developed. Undesirable features of the medicinal chemistry and second-generation synthesis methods were avoided by employing the aldol reaction, pyridazinone ring formation, *N*-alkylation reaction, and recrystallization conditions. From **8** was manufactured 26.3 kg of pyridazinone **11** in 76% yield in a practical operation, representing an increase of 11% in comparison with that using the second-generation synthesis. During manufacturing, impurities were well controlled at low levels in all steps. As a consequence, 30.6 kg of the highly pure

Scheme 3. Formation of the impurity A



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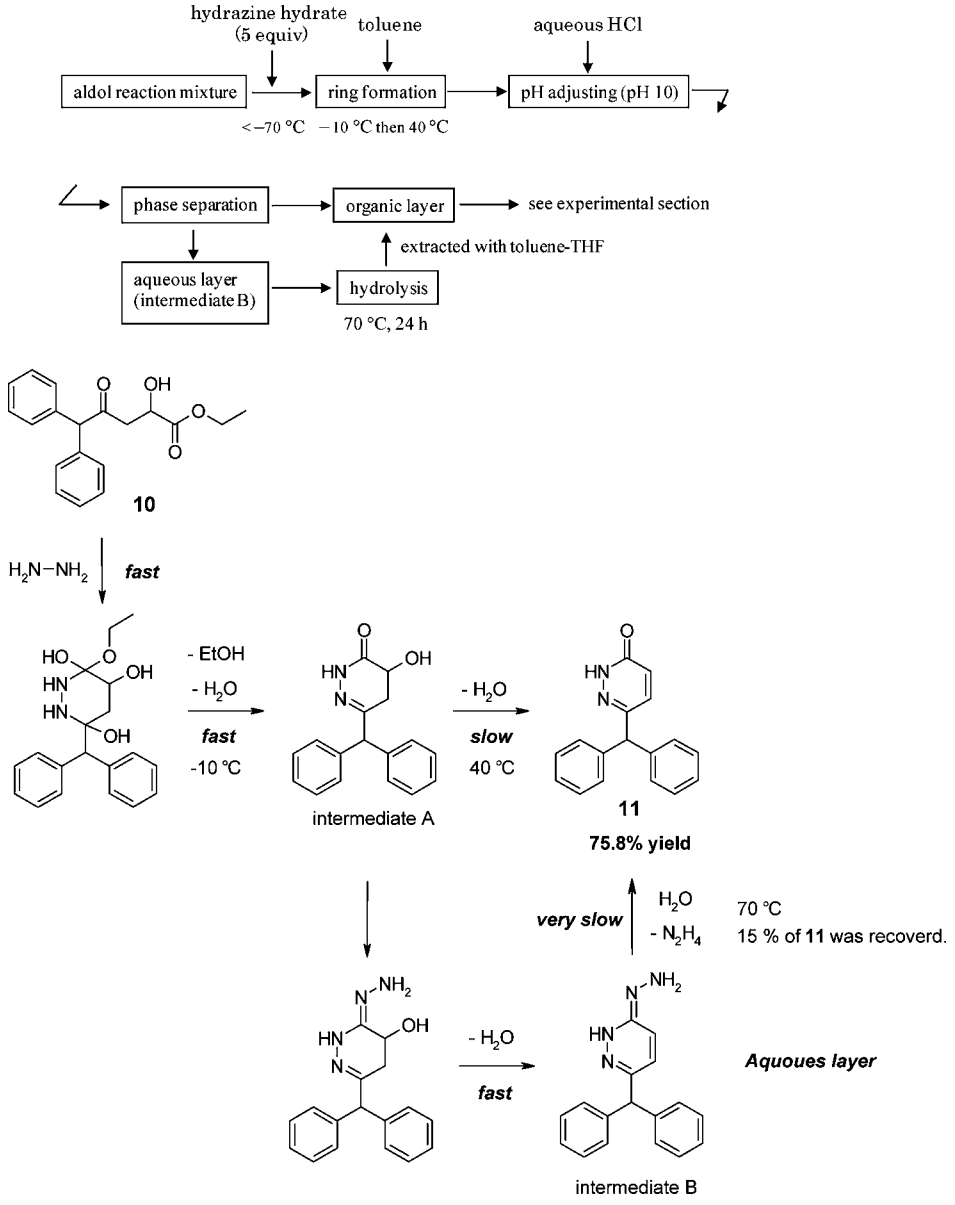

Figure 4. One-pot procedure for the preparation of pyridazinone ring formation.

Table 2. Base screening for *N*-alkylation step

		HPLC area %[a]				
entry	conditions	**11**	**12**	**1**	unknown impurity	comments
1[b]	LiH (3 equiv) DMF, 25 °C, 48 h	2.7	80.1	<1	<0.5	former method
2[b]	K_2CO_3 (2.4 equiv) DMF, 70 °C, 48 h	7.4	78.9	<1	2.1	–
3[b]	*t*-BuOK (1.1 equiv) DMF, 25 °C, 48 h	2.5	73.3	2.9	7.3	–
4	EtONa (1 equiv) EtOH, 50 °C, 48 h	3.4	70.8	<1	6.2	–
5	KOH (1 equiv) EtOH, 50 °C, 48 h	5.1	76.0	5.9	1.1	–
6	NaOH (1 equiv) EtOH, 50 °C, 48 h	2.0	82.0	3.9	<0.5	the best condition; used in next step without isolation

[a]Determined by HPLC method A (see Experimental Section). [b]Large amount of toluene was required for the extraction of **12**.

drug substance **1** was prepared for GMP delivery. Overall yield was improved from 34.9% with the second-generation method to 51.1% with the first scale-up synthesis.

■ EXPERIMENTAL SECTION

General. Starting materials, reagents and solvents were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in the specified deuterated solvent. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual solvent ($CHCl_3$ 7.26 ppm; DMSO-d_6 2.50 ppm) or TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet doublet, t = triplet, q = quartet, m = multiplet, and br =

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Scheme 4. Synthesis of crude 1

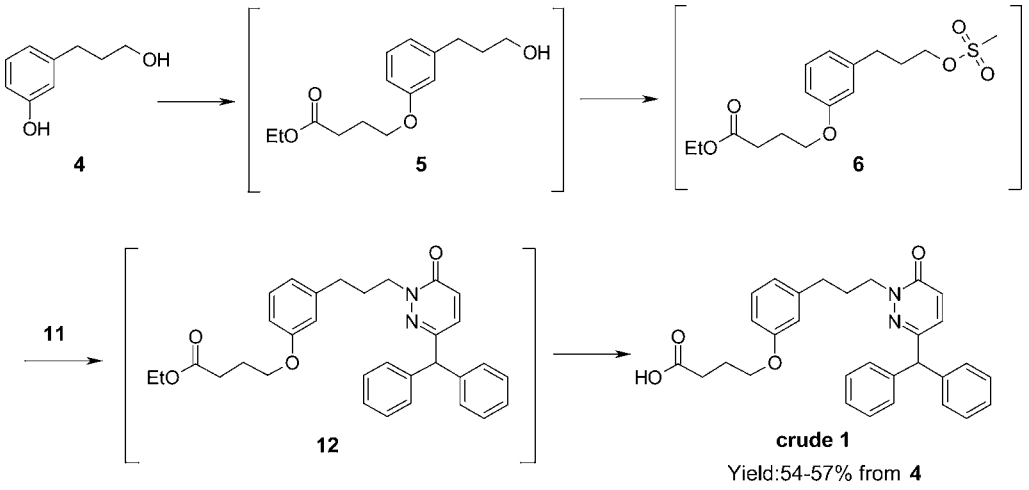


Table 3. Solvent selection for recrystallization step[a]

entry	solvent (15 w/v)	purity of **1** (%)[b]	loss to the filtrate (%)[b]
1	*i*-PrOH/water =1:1	99.7	1.8
2	EtOH/water =1:1	99.0	3.9
3	acetone/water =1:1	97.7	8.8

[a]Purity of **crude 1** = 97.0%, temperature = 0 °C. [b]Determined by HPLC method A (see Experimental Section).

broad), coupling constant (Hz), and integration. Chemical shifts of proton-decoupled ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.0 ppm), DMSO-d_6 (39.5 ppm) on the δ scale. HPLC was performed using a HITACHI D-2500 or D-7500 system. HPLC methods are described below.

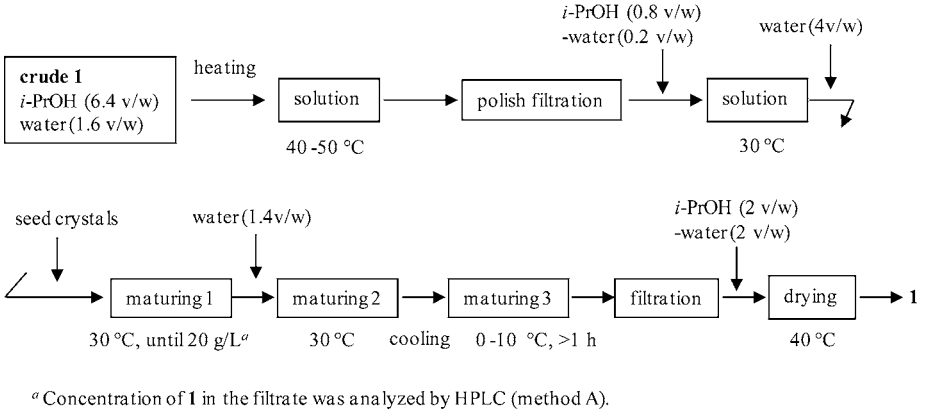
HPLC Methods. *Method A.* Waters, XBridge C18, 3.5 μm, 4.6 mm ×150 mm column, elution 0.05 M KH_2PO_4 aq/CH_3CN = 4:6, over 30 min, 1.0 mL/min, at 40 °C, with UV detection at 235 nm.

8: 4.6 min, intermediate A: 2.2 min, intermediate B: 1.4 min, **10**: 3.2 min, **11**: 2.5 min, **6**: 4.2 min, **12**: 15.4 min, **1**: 4.4 min.

Method B. Waters XTerra MS C8, 3.5 μm, 4.6 mm ×150 mm column, elution 0.05 M K_2HPO_4 (adjust pH 8.0 by aq H_3PO_4)/CH_3CN = 6/4,over 45 min, 1.0 mL/min, at 25 °C, with UV detection at 235 nm.

4: 2.1 min, **5**: 6.0 min, **6**: 12.9 min.

6-Benzhydryl-2,3-dihydropyridazin-3-one (11). Preparation of LDA solution was as follows. To a solution of diisopropylamine (14.7 kg, 145.3 mol) in THF (135 kg) was added *n*-BuLi (15% in *n*-hexane, 62.2 kg, 145.3 mol) at −30 to −5 °C, and the mixture was aged for 1 h. The batch was cooled to −78 °C. To a solution of LDA, a solution of 1,1-diphenylacetone (**8**) (27.8 kg, 132.2 mol) in THF (70.1 kg) was added below −70 °C (−78 to −73 °C), and the mixture was aged for 1 h. To the mixture was added ethyl glyoxylate **9** (54.1 kg, 265.0 mol, polymer type, 50% solution in toluene) below −70 °C (−78 to −76 °C), and the mixture was aged for 0.5 h, after which time HPLC analysis indicated that <1% starting material **8** remained (HPLC method A). To the batch was added hydrazine hydrate (33.1 kg, 661.2 mol) below −70 °C. The reaction mixture was poured into toluene (20.1 kg) followed by washing with THF (13.1 kg) and toluene (12.0 kg) at −10 °C. The batch was aged for 12 h, after which time HPLC analysis indicated that <1% compound **10** remained (HPLC method A). The batch was warmed to 40 °C and aged for 3 h, after which time HPLC analysis indicated that <1% intermediate A remained (HPLC method A). To the batch was added water (139 kg) and toluene (40.0 kg). To the solution was added 6 N HCl (32.7 kg), and pH was adjusted to 10.1. The resulting organic layer was washed twice with a 20% (w/w) aqueous solution of NaCl (28 L). These aqueous layers were combined, heated to 70 °C, and aged for 24 h, after which time



[a] Concentration of **1** in the filtrate was analyzed by HPLC (method A).

Figure 5. Procedure for recrystallization step.

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Table 4. Quality of crude 1 and 1

		HPLC area %[a]								
entry		1.6	2.0	2.3	2.4	4.0	4.4 (1)	5.5	6.9	13.3
1	crude 1	0.7	0.2	0.2	0.8	0.3	97.0	0.2	0.2	0.3
2	1	N.D.	N.D.	N.D.	0.05	0.11	99.7	0.14	N.D.	N.D.

[a]Retention time on HPLC is described (min), as determined by HPLC method A (see Experimental Section).

HPLC analysis indicated that <1% intermediate B remained (HPLC method A). To the mixture was added THF (25.0 kg), toluene (96.0 kg) and a 20% (w/w) aqueous solution of NaCl (28 L). The resulting organic layer was combined with the former organic layer and concentrated *in vacuo* to 82 L. To the resulting residue was added *n*-heptane (57.0 kg) for 1 h, and the mixture was aged for 2 h. The resulting slurry was filtered and washed with a solution of toluene (29.0 kg) and *n*-heptane (34.0 kg). The wet cake was dried *in vacuo* at 40 °C to afford the desired **11** with 97% purity via HPLC method A (26.3 kg, 75.8% yield from **8**).

An analytical sample of **10** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 1:1).

*Compound **10***. ESI-MS: *m/z* 335 $(M + Na)^+$.

^1H NMR (400 MHz, DMSO-d_6): δ 7.15−7.40 (10H, m), 5.62 (1H, d, *J* = 6.0 Hz), 5.40 (1H, s), 4.35−4.45 (1H, m), 4.05 (2H, q, *J* = 7.1 Hz), 2.75−2.95 (2H, m), 1.14 (3H, t, *J* = 7.1 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 207.1, 173.1, 138.0 (2 carbons), 129.1 (4 carbons), 128.2 (4 carbons), 127.5 (2 carbons), 66.1, 63.8, 62.5, 47.4, 14.5.

*Compound **11***. ESI-MS: *m/z* 263 $(M+H)^+$.

^1H NMR (400 MHz, $CDCl_3$): δ 11.93 (1H, s), 7.10−7.40 (11H, m), 6.88 (1H, d, *J* = 9.7 Hz), 5.44 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 150.0, 140.7, 134.5, 130.2 (2 carbons), 129.1 (4 carbons), 128.8 (4 carbons), 127.3 (2 carbons), 55.9.

Ethyl 4-[3-(3-hydroxypropyl)phenoxy]butanoate (5). To a solution of 3-(3-hydroxypropyl)phenol (**4**) (19.0 kg, 124.8 mol) in DMF (90.0 kg) at 25 °C were added ethyl 4-bromobutanoate (30.2 kg, 154.8 mol) and potassium carbonate (25.9 kg, 187.4 mol). The batch was warmed to 85−90 °C, and the mixture was aged until compound **4** < 1% in the reaction mixture (HPLC check, this usually takes 60 h, HPLC method B). The batch was cooled to 25 °C, and toluene (115.2 kg) and water (190.0 kg) were added. To the batch was added a 17.5% aqueous solution of HCl (35% aqueous HCl 8.4 kg/water 7 kg), and pH was adjusted to 8.3. The resulting organic layer was washed with a 20% (w/w) aqueous solution of NaCl (38.0 L) and concentrated *in vacuo* to afford the desired compound **5**. This was mixed with toluene (95.0 kg), and this solution was used in the next step without purification. An analytical sample of **5** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 2:1).

ESI-MS: *m/z* 267 $(M + H)^+$.

^1H NMR (400 MHz, DMSO-d_6): δ 7.11 (1H, t, *J* = 7.8 Hz), 6.60−6.72 (3H, m), 4.40 (1H, t, *J* = 5.0 Hz), 4.02 (2H, dd, *J* = 14.0, 6.8 Hz), 3.91 (2H, t, *J* = 6.4 Hz), 3.35 (2H, dd, *J* = 11.2, 6.4 Hz), 2.52 (2H, t, *J* = 7.8 Hz), 2.40 (2H, t, *J* = 7.4 Hz), 1.85−1.97 (2H, m), 1.55−1.72 (2H, m), 1.13 (3H, t, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 173.1, 156.0, 144.3, 129.7, 121.1, 115.0, 112.1, 66.8, 60.6, 60.4, 34.7, 32.2, 30.7, 24.8, 14.6.

Ethyl 4-{3-[3-(mesyloxy)propyl]phenoxy}butanoate (6). To a solution of **5** in toluene were added Et_3N (22.7 kg, 224.3 mol) and toluene (4.0 kg). The batch was cooled to 5 °C, and methanesulfonyl chloride (18.6 kg, 162.4 mol) was added, followed by washing with toluene (3.0 kg). The reaction mixture was aged for 3 h at 10 °C, after which time HPLC analysis indicated that <1% compound **5** remained (HPLC method B). To the batch was added water (95.0 kg), and the resulting organic layer was washed with a 20% (w/w) aqueous solution of NaCl (38.0 L). The resulting organic layer was concentrated *in vacuo* to 57 L. To the residue was added EtOH (22.0 kg), and the resulting solution was used in the next step without purification. An analytical sample of **6** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 2:1).

ESI-MS: *m/z* 345 $(M + H)^+$.

^1H NMR (400 MHz, DMSO-d_6): δ 7.15 (1H, t, *J* = 8.0 Hz), 6.65−6.77 (3H, m), 4.15 (2H, t, *J* = 6.2 Hz), 4.02 (2H, dd, *J* = 14.4, 7.2 Hz), 3.92 (2H, t, *J* = 15.4 Hz), 3.13 (3H, s), 2.52−2.62 (2H, m), 2.40 (2H, t, *J* = 7.4 Hz), 1.85−1.98 (4H, m), 1.14 (3H, t, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ 173.1, 159.1, 142.9, 129.9, 121.1, 115.0, 112.5, 70.2, 66.8, 60.4, 37.1, 31.5, 30.7, 30.6, 24.8, 14.6.

Ethyl 4-{3-[3-(3-benzhydryl-6-oxo-1,6-dihydropyridazin-1-yl)propyl]phenoxy}butanoate (12). To a solution of **6** in EtOH was added compound **11** (24.0 kg, 91.5 mol). To the batch was added a solution of NaOH in EtOH (NaOH: 6.0 kg, 150.0 mol in EtOH: 150.0 kg) followed by washing with EtOH (8.0 kg). The batch was warmed to 50−65 °C and aged for 48 h, after which time HPLC analysis indicated that <2% compound **6** remained (HPLC method A). This reaction mixture, which contained **12**, was used in the following hydrolysis.

An analytical sample of **12** was purified by SiO_2 column chromatography (*n*-heptane/EtOAc = 4:3).

ESI-MS: *m/z* 511 $(M+H)^+$.

^1H NMR (400 MHz, DMSO-d_6): δ 7.25−7.31 (6H, m), 7.15−7.23 (6H, m), 6.84−6.87 (1H, m), 6.60−6.70 (3H, m), 5.51 (1H, s), 4.01−4.05 (2H, m), 3.88−3.98 (4H, m), 2.38−2.43 (4H, m), 1.85−2.00 (4H, m), 1.12 (3H, t, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ173.1, 159.4, 159.2, 148.9, 143.5, 141.9 (2 carbons), 133.9, 130.2 (2 carbons), 130.1 (2 carbons), 129.7 (2 carbons), 129.4 (2 carbons), 129.0 (2 carbons), 127.3, 121.1, 115.0, 112.5, 66.8, 60.4, 55.2, 50.5, 32.7, 31.8, 30.7, 29.9, 25.0, 14.9.

Crude 4-{3-[3-(3-Benzhydryl-6-oxo-1,6-dihydropyridazin-1-yl)propyl]phenoxy}butanoic acid (Crude 1). To the reaction mixture that contained compound **12** was added water (114.0 kg) and a 25% (w/w) aqueous solution of NaOH (14.0 kg, 87.5 mol) at 30 °C. The batch was aged for 4 h at 40 °C, after which time HPLC analysis indicated that <0.5% compound **12** remained (HPLC method A). This reaction mixture was cooled to 5−10 °C, and a 17.5% (w/w) aqueous solution of HCl was added, and pH was adjusted to 1.4. To the batch was added toluene (248.0 kg). The resulting organic layer

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was concentrated *in vacuo* to 57 L. To the residue was added EtOAc (86.0 kg), and the mixture was concentrated *in vacuo* to 57 L. To the resulting residue was added EtOAc (34.0 kg), *n*-heptane (24.0 kg) and seed crystals of **1** (40.0 g). The mixture was concentrated *in vacuo* to 57 L, and to the residue was added EtOAc (17.0 kg) and *n*-heptane (22.5 kg). The resulting slurry was aged for 2 h at 10 °C and filtered, followed by washing with a solution of EtOAc (27.0 kg)/*n*-heptane (21.0 kg). The wet cake was dried *in vacuo* at 40 °C to afford the desired **crude 1** with 97% purity via HPLC method A (32.7 kg, 54.3% yield from **4**).

4-{3-[3-(3-Benzhydryl-6-oxo-1,6-dihydropyridazin-1-yl)propyl]phenoxy}butanoic acid (1). The mixture of **crude 1** (32.5 kg, 67.3 mol) in *i*-PrOH (163.3 kg) and water (52.0 kg) was warmed to 40−50 °C. The resulting solution was filtered through a 0.45 μm filter into another vessel, followed by washing with a solution of *i*-PrOH (20.4 kg)−water (6.5 kg). To the resulting filtrate was added water (141.6 kg) for 3 h at 30 °C. To the batch was added seed crystals of **1** (32.5 g), and the mixture was aged for 2 h at 30 °C. In this stage, the concentration of compound **1** in filtrate was 8.81 g/L, as determined by HPLC. To the resulting slurry was added water (33.9 kg) for 0.5 h at 30 °C, and the mixture was cooled to 0−10 °C and aged for 13 h. The slurry was filtered and washed with a solution of *i*-PrOH (51.0 kg)−water (65.0 kg) that was prefiltered through a 0.45 μm filter. The wet cake was dried *in vacuo* at 40 °C to afford the desired **1** with 99.7% purity as determined by HPLC method A (30.6 kg, 94.2% yield).

ESI-MS: m/z 483 $(M + H)^+$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (1H, br), 7.23−7.52 (6H, m), 7.11−7.21 (6H, m), 6.83−6.87 (1H, m), 6.65−6.70 (3H, m), 5.51 (1H, s), 3.97 (2H, t, J = 7.0 Hz), 3.90 (2H, t, J = 6.4 Hz), 2.30−2.38 (4H, m), 1.85−1.95 (4H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ 174.7, 159.3, 159.1, 148.8, 143.3, 141.8 (2 carbons), 133.7, 130.0 (2 carbons), 129.8 (2 carbons), 129.5 (2 carbons), 129.3 (2 carbons), 129.0 (2 carbons), 127.3, 121.1, 114.9, 112.3, 66.9, 55.4, 55.2, 50.4, 32.5, 30.7, 29.9, 24.8.

Anal. Calcd for $C_{30}H_{30}N_2O_4$. Calcd: C (74.67%), H (6.27%), N (5.81%). Found: C (74.57%), H (6.28%), N (5.77%).

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Notes

The authors declare no competing financial interest.

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