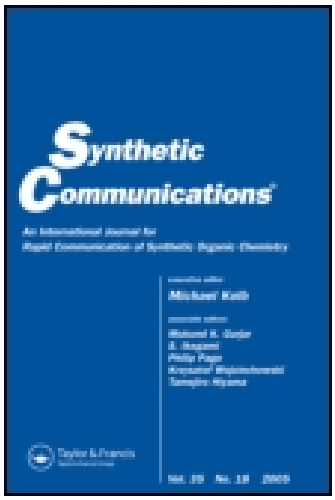

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A Practical Procedure for the Synthesis of Esonarimod, (*R*,*S*)-2-Acetylthiomethyl-4-(4-methylphenyl)-4-oxobutanoic Acid, an Antirheumatic Agent. II[#]

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ABSTRACT

An efficient large-scale synthesis of Esonarimod, (*R*,*S*)-2-acetylthiomethyl-4-(4-methylphenyl)-4-oxobutanoic acid (**1**), a new antirheumatic drug, was established. A small amount of water increased the yield of the Michael addition of thioacetic acid (**4**) to 2-methylene-4-(4-methylphenyl)-4-oxobutanoic acid (**2**) to give **1**. Multikilogram amounts of **1** (over 25 kg) were successfully obtained using this

[#]See Ref. [1]

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procedure. In addition, this procedure was repeated nine times, and reproducible results were obtained.

Key Words: Esonarimod; Antirheumatic drug; Friedel–Crafts acylation; Michael addition; Process chemistry.

INTRODUCTION

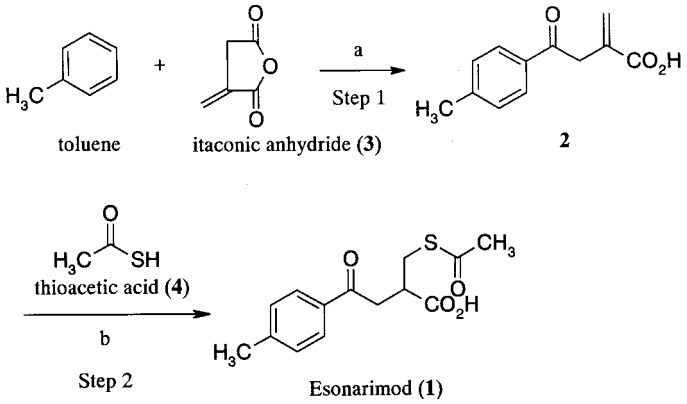
We have previously developed Esonarimod, (*R,S*)-2-acetylthiomethyl-4-(4-methyl phenyl)-4-oxobutanoic acid (**1**), as a new antirheumatic drug.[2–4] To support further pharmacological evaluation and clinical trials, a large-scale synthesis of **1** was required. In our previous article,[1] an efficient process with regard to the large-scale synthesis of **1** was established at a 60-grams scale. However, this procedure was not completely satisfactory and required further improvement for larger-scale production. In this article, we report the results of extensive laboratory studies and a pilot plant study (over 25-kilogram scale).

RESULTS AND DISCUSSION

Synthesis of 2 (Step 1) in the Laboratory

In our previous article,[1] the synthesis of **1** was reported as follows. The synthetic procedure of **1** is outlined in Sch. 1. 2-Methylene-4-(4-methylphenyl)-4-oxobutanoic acid (**2**) was obtained by Friedel–Crafts acylation of toluene with commercially available itaconic anhydride (**3**) in the presence of aluminum trichloride ($AlCl_3$) and nitrobenzene in 63% yield. Compound **1** was obtained in 74% yield by the Michael addition of thioacetic acid (**4**) to **2** in the presence of triethylamine and toluene. Additionally, **1** was recrystallized from isopropylether (IPE) for purification. The overall yield of **1** was 47% from **3**. However, the reaction conditions of each step were not enough studied. Then the amount of reagents and the reaction temperature were investigated in laboratory studies.

The reaction conditions for the first step were investigated about the amount of $AlCl_3$ and toluene, and reaction temperature in the present study, and the results are shown in Table 1. These results are consistent with the fact that the amount of $AlCl_3$ should be 2.0 equivalents (Entries 1–4), and toluene gave good results at 1.7 equivalents (Entries 3, 5–8). When the amount of toluene increased, by-product **5**



Scheme 1. (a) $AlCl_3$, nitrobenzene, 50°C, 40 min, 63%; (b) Et_3N, toluene, 60°C, 4 h, 74%.

Table 1. Conditions for the synthesis of **2**.

	Conditions			**2**		
Entry	$AlCl_3$ (equiv.)	Toluene (equiv.)	Temperature (°C)	Yield (%)	Purity (area%)	By-product **5** (area%)
1	1.0	1.7	50	29.5	99.36	—
2	1.5	1.7	50	60.0	99.34	—
3	2.0	1.7	50	68.4	99.36	—
4	3.0	1.7	50	67.8	99.45	—
5	2.0	1.1	50	64.7	99.49	—
6	2.0	2.3	50	68.2	99.39	—
7	2.0	2.9	50	69.6	97.77	1.69%
8	2.0	5.7	50	70.8	95.74	3.67%
9	2.0	1.7	40	69.1	99.18	—
10	2.0	1.7	70	62.0	99.12	—

All reactions were conducted on a 28 g (**3**) scale.
All reaction times were fixed at 2 h.
$AlCl_3$, **3**, and toluene were added under 20°C.
The purity of **2** and **5** were determined by HPLC.

was formed (Entries 7, 8).[1,5] The structure of **5** is shown in Fig. 1. In the previous article,[1] five by-products, **6–9** were reported in this reaction (Fig. 1). However, these compounds except **5** were not detected. When the reaction temperature was 50°C, the yield and purity of **2** were

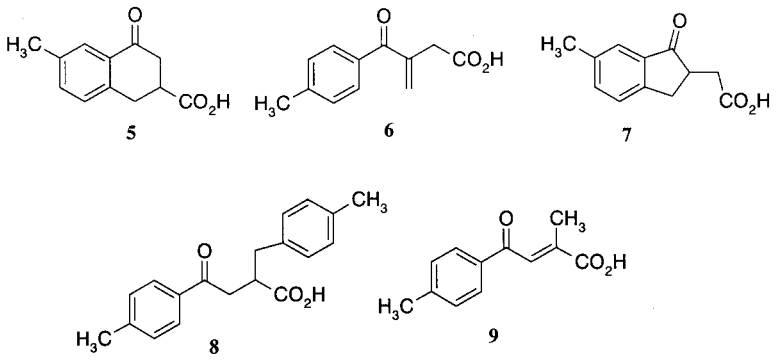


Figure 1. Structure of by-products.

Table 2. Reaction temperature during the addition of reagents for step 1.

	The addition temperature (°C)				**2**	
Entry	$AlCl_3$	**3**	Toluene	HCl	Yield (%)	Purity (area%)
1	20	24	32	18	69.1	99.11
2	30	24	32	18	71.8	99.20
3	36	40	40	18	70.4	99.33
4	47	49	48	18	68.0	99.05
5	47	48	55	85	66.9	99.69

All reactions were conducted on a 20 g (**3**) scale.
$AlCl_3$: 2.0 equivalents, toluene : 1.7 equivalents,
HCl: conc. HCl (50 mL) and H_2O (200 mL).
The addition temperature indicates the reaction temperature during the addition of reagents to the reaction mixture.
The purity of **2** was determined by HPLC.

similar to those at 40°C (Entry 9). When the temperature was raised to 70°C, the yield of **2** decreased. However, the purity of 2 did not come down (Entry 10).

The addition of the reagents, such as $AlCl_3$, **3**, and toluene, to the reaction mixture was exothermic. Therefore, the reagents should be added to the reaction mixture slowly in portions with cooling. The reaction temperature should be kept above the freezing point of nitrobenzene (8°C). Therefore, we investigated the acceptable temperature level during the addition of these reagents. The results are shown in Table 2. Three

Table 3. Amount of toluene and cooling temperature for isolation of **2**.

		Cooling		**2**	
Entry	Toluene for for dilution (mL)	Temperature (°C)	Time (min)	Yield (%)	Purity (area%)
1	360	0	20	60.6	99.45
2	360	−8	20	63.5	99.50
3	360	−15	20	64.7	99.49
4	360	−15	60	67.0	99.36
5	720	−15	20	69.3	99.20
6	2160	−15	20	69.6	99.27

All reactions were conducted on a 56 g (**3**) scale.
$AlCl_3$: 2.0 equivalents, toluene: 1.7 equivalents.
HCl: conc. HCl (100 mL) and H_2O (400 mL).
The purity of **2** was determined by HPLC.

mol/L hydrochloric acid was added to the reaction mixture for work-up, and this was also an exothermic process. The effects of the temperature were also examined.

Within the limits of Table 2, all of yield and purity of **3** were almost the same. The reaction temperature during the addition of $AlCl_3$, **3**, and toluene to the reaction mixture should be kept below 50°C. The temperature for the addition of aqueous hydrochloric acid at work-up should be below 85°C. The reaction temperature was well controlled with stirring. In the study of Table 2, by-product **5** was not detected. Then the production of **5** seemed to independent of temperature.

The isolation of **2** from the reaction mixture was then examined. The cooling temperature and amount of toluene for dilution were investigated. The results are shown in Table 3.

The purity of **2** was almost the same for all of the conditions examined in Table 3. When the reaction mixture was cooled to −15°C, **2** was obtained in higher yield than at 0°C (Entry 3). There was no difference in the yield and purity of **2** with a change in the cooling duration (Entries 3, 4). The addition of a large amount of toluene for dilution also had little effect.

Synthesis of 1 (Step 2) in the Laboratory

The reaction conditions for the Michael addition of **4** to **2** were investigated for larger-scale preparation of **1**, and the results are shown in Table 4.

Table 4. Conditions for the synthesis of crude esonarimod (**1**).

	Conditions				Crude **1**	
Entry	**4** (equiv.)	Et_3N (equiv.)	H_2O (equiv.)	Temperature (°C)	Yield (%)	Purity (area%)
1	1.2	0.2	—	60	81.9	98.53
2	1.2	0.2	2.5	60	88.8	98.86
3	1.2	0.2	5	60	89.0	98.81
4	1.2	0.2	10	60	89.0	99.05
5	1.0	0.2	5	60	86.3	98.07
6	1.5	0.2	5	60	86.8	98.99
7	2.0	0.2	5	60	82.2	99.06
8	1.2	—	5	60	76.9	82.58
9	1.2	0.1	5	60	89.1	98.93
10	1.2	0.3	5	60	88.0	98.85
11	1.2	0.4	5	60	88.7	98.83
12	1.2	0.2	5	40	86.7	98.99
13	1.2	0.2	5	50	90.1	98.82
14	1.2	0.2	5	70	86.6	98.46
15	1.2	0.2	5	80	80.0	98.80

All reactions were conducted on a 20 g (**2**) scale.
Toluene (solvent): 121 mL.
All of the reaction times were fixed at 4 h.
The purity of **1** was determined by HPLC.

When the reaction of **2** and **4** was carried out in the presence of 0.2 equivalents of triethylamine (Et_3N) at 60°C for 4 h, **1** was obtained in 81.9% yield with 98.53% purity, whereas the addition of 2.5 equivalents of water to the reaction mixture increased the yield of **1** up to 88.8% (Entries 1, 2). A similar effect was observed with the addition of 5–10 equivalents of water (Entries 3, 4). This suggested that the addition of some water might improve the yield of the Michael addition, although the mechanism is not yet clear. Thus, it is possible that wet **2** could be used for this reaction. This would save the time and labor needed for drying, and would be preferable during manufacture at a pilot plant. The addition of 1.2 equivalents of **4** to **2** gave a slightly better yield than 1.0 or 1.5 equivalents (Entries 3, 5, and 6). Compound **1** could be obtained without Et_3N, but the yield and purity of **1** were both decreased (Entry 8). The addition of 0.1 to 0.4 equivalents of Et_3N did not significantly affect the yield (Entries 3, 9–11). Reaction temperature of 50°C and 60°C gave

similar results. However, at temperatures of 40, 70, and 80°C, the yield of **1** declined though the purity was unchanged (Entries 3, 12–15).

To purify the crude product **1**, recrystallization from IPE was employed.[1] As shown in Table 4, the purity of crude **1** was so high that the main purpose of purification was to remove residual toluene, which was the solvent used for this step. Crude **1** (20.0 g, purity: 99.53%) (Table 4, Entry 1) was recrystallized from 200 mL of IPE, and stirred at −15°C for 30 min to give 18.6 g (93.1%) of **1**. Its purity was 99.70%. The overall yield of **1** was 59.5% from **3** in the laboratory.

Synthesis of 1 in a Pilot Plant

Considering the above observations, we tried to synthesize **1** on a pilot plant scale. A 20 kg sample of **3** was used as a starting material. The procedure is illustrated in Fig. 2.

Two equivalents of $AlCl_3$ were used as the catalyst for the Friedel–Crafts reaction according to the results obtained in Table 1. The synthesis of **2** was carried out nine times by changing the amount of toluene

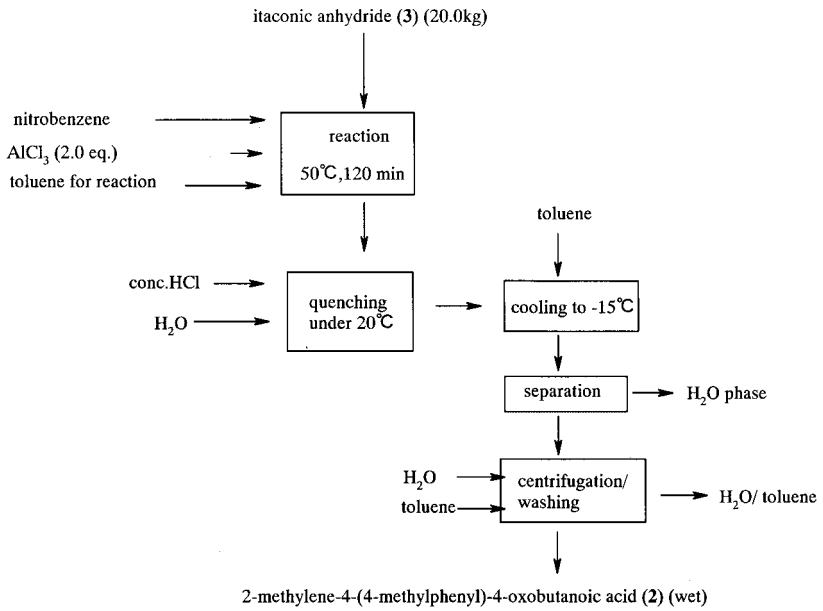


Figure 2. Synthetic diagram for **2**.

Table 5. Synthesis of **2** (step **1**) in a pilot plant.

		2				
Entry	Toluene (equiv.)	Wet weight (kg)	Dry weight (kg)	Yield (%)	Purity (area%)	By-product **5** (area%)
1	1.7	31.0	23.8	65.5	96.22	3.30
2	1.7	32.3	25.4	69.5	97.47	2.30
3	1.4	34.6	27.1	74.2	99.68	—
4	1.4	33.2	26.5	72.5	99.75	—
5	1.4	30.4	24.2	66.6	99.50	0.20
6	1.4	30.7	25.3	69.8	99.64	0.10
7	1.4	32.3	25.6	70.0	98.32	1.20
8	1.4	32.9	26.2	71.7	99.68	—
9	1.4	30.3	25.1	69.2	99.78	—

All reactions were conducted on a 20-kg (**3**) scale.
$AlCl_3$: 2.0 equivalents.
The purity of **2** and **5** were determined by HPLC.

to identify reaction conditions that would avoid the formation of by-product **5**. The results are shown in Table 5.

When 1.7 equivalents of toluene were used in the laboratory, **5** was not obtained. However, at a 20 kg scale, **5** was produced (Entries 1, 2). The reaction temperature was independent of **5** from Table 2. Although the reason for this result was not clear, the amount of toluene seemed to play a role in the formation of **5**. While by-product **5** was not always produced when 1.4 equivalents of toluene were used (Entries 3–9), small amount of **5** were formed under the conditions in Entries 5–7. These problems will need to be solved before future larger-scale synthesis. In all cases, the purity of 2 was quite good except for the production of **5**. However the yield of **2** had some variation, which may also be a problem for the stable supply of this substance.

The second step is the synthesis of **1**. We used **2** without drying, since the presence of water gave better results than non-water conditions in the Michael reaction of **2** with **4** in the laboratory. The procedure is illustrated in Fig. 3.

The synthesis of crude **1** was carried out nine times, and the results are shown in Table 6.

In the large-scale synthesis of **1**, the ratio of the reactants (**2:4**:Et_3N) was fixed at 1.0:1.2:0.2. Furthermore, the reaction temperature was 60°C based on the results of the laboratory examinations (Table 4). Although

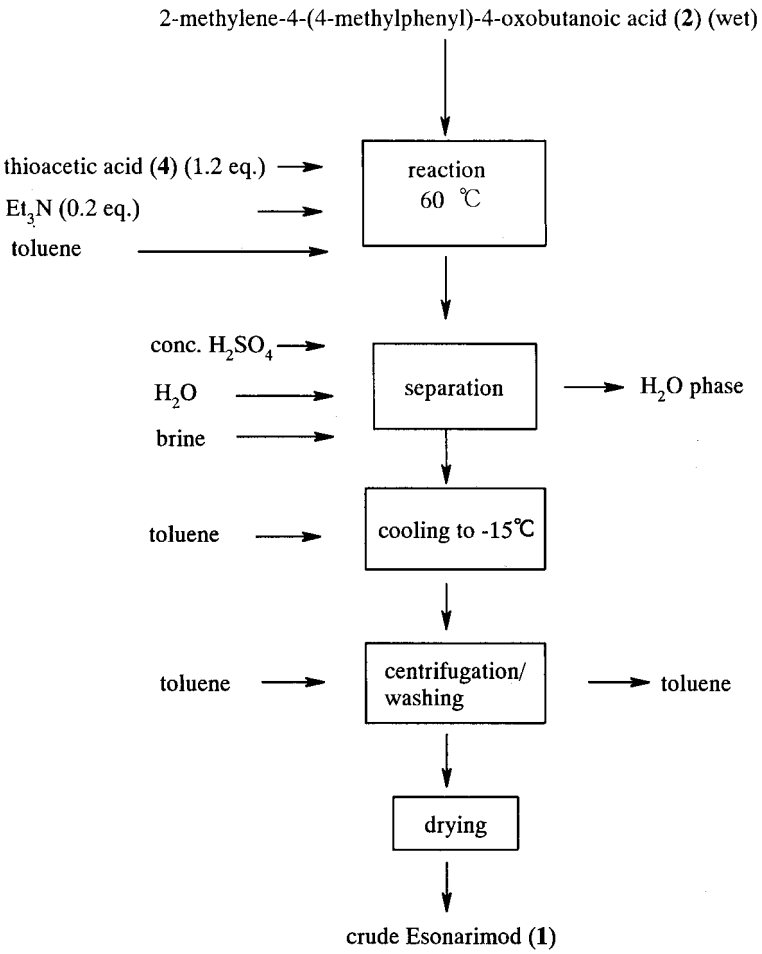


Figure 3. Synthetic diagram for esonarimod (**1**).

the reaction time was shortened to 2 h based on Entry 5, this had no effect on the yield and purity of crude **1**. The yield and purity were almost the same as in the laboratory examination and each lot had a comparatively stable yield and purity. By-product **5** (1.6–0.9%) produced in Step 1 was not removed by this procedure (Entries 1, 2). However, a slight amount of **5** could be removed (Entries 5–7).

The purification of **1** is illustrated in Fig. 4. This step was carried out nine times and the results are shown in Table 7.

Table 6. Synthesis of crude esonarimod (**1**).

	2			Crude **1**		
Entry	Wet (kg)	Dry (kg)	Reaction time (h)	Yield (%)	Purity (area%)	By-product **5** (area%)
1	30.5	23.4	4	87.1	98.17	1.61
2	31.8	25.0	4	87.3	98.82	0.93
3	34.1	26.7	4	88.9	99.67	—
4	32.7	26.1	4	88.6	99.85	—
5	29.8	23.8	2	87.1	99.62	—
6	30.2	24.9	2	87.3	99.65	—
7	31.8	25.1	2	87.9	99.58	—
8	32.8	26.2	2	88.4	99.67	—
9	29.8	24.7	2	80.0	99.81	—

4: 1.2 equivalents, Et_3N: 0.2 equivalents.
The purity of **1** and **5** were determined by HPLC.

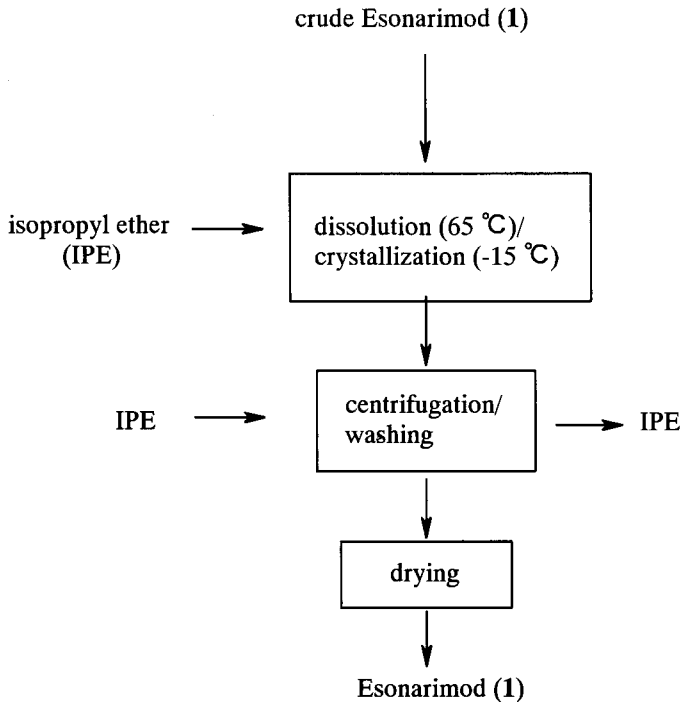


Figure 4. Purification diagram of esonarimod (**1**).

Table 7. Purification of esonarimod (**1**).

Entry	Crude **1** (kg)	Purified **1**		By-product **5** (area%)
		Yield (%)	Purity (area%)	
1	27.8	90.0	98.62	1.29
2	29.8	90.9	99.91	0.01
3	32.5	89.8	99.90	—
4	31.6	92.4	99.92	—
5	28.4	88.4	99.83	—
6	29.6	91.9	99.84	—
7	30.1	91.6	99.85	—
8	31.8	90.7	99.80	—
9	30.5	90.3	99.87	—

The purity of **1** and **5** were determined by HPLC.

The pilot plant results were as good as those in the laboratory and each lot of **1** had a comparatively stable yield and purity. However, **5** produced in Step 1 was not removed in this step (Entry 1). Upon the second recrystallization of **1** (Entry 1), 22.8 kg of **1** was obtained. The rate of recovery was 91.8%, the purity was 99.88%, and the yield of **5** was 0.01%. The best overall yield of 1 was 59.2% from **3** (Tables 5–7, Entry 3), which was almost the same result as at a laboratory scale (59.5%).

CONCLUSIONS

An effective and convergent process for the synthesis of Esonarimod (**1**) from toluene and itaconic anhydride (**3**) has been examined. This method gives 2-methylene-4-(4-methylphenyl)-4-oxobutanoic acid (**2**) and **1** in high yield and high purity. The presence of some water increased the yield in the Michael addition of thioacetic acid (**4**) to **2**. At a laboratory scale, **1** was obtained in a higher overall yield than in the initial synthesis (59.5% from commercially available itaconic anhydride (**3**) vs. 47%).

Multikilogram amounts of **1** (over 25 kg) were successfully obtained using this procedure. The overall yield of **1** from **3** was almost the same as

that in the laboratory (59.2% vs. 59.5%). Furthermore, the procedure was repeated nine times, and reproducible results were obtained.

EXPERIMENTAL

General

Melting points were determined by a Buchi 535 melting point apparatus and were uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1760 spectrometer. ^{1}H-NMR spectra were recorded on a Varian VXL-200 or VXR-300 spectrometer. Chemical shifts are reported in ppm (δ) values, as determined using a JEOL JMS-SIX102 spectrometer. TLC was performed on silica gel pre-coated plates (Merck, Kieselgel $60F_{254}$). Spots and bands were detected by UV irradiation (254 nm). HPLC was performed on an ODS-80 TM column (Tosoh, 4.6×150 mm) with 250 nm. Itaconic anhydride, $AlCl_3$, and thioacetic acid were obtained commercially.[6–8]

Synthesis of 1 in Laboratory

2-Methylene-4-(4-methylphenyl)-4-oxobutanoic acid (2). Aluminum chloride (powder type) (66.7 g, 500 mmol) was added portionwise to nitrobenzene (80 mL) at 20°C. After stirring for 20 min, itaconic anhydride (3) (28.0 g, 250 mmol) was added and toluene (39.2 g, 425 mmol) was added dropwise over 20 min at 20°C. The reaction mixture was stirred at 50°C for 120 min, and then poured into conc. hydrochloric acid (50 mL) –water (200 mL) at 20°C. Toluene (180 mL) was added, the mixture was stirred at −15°C for 20 min, and the precipitate was collected by filtration. The precipitate was washed with 3 mol/L hydrochloric acid (50 mL), water (50 mL, twice), and toluene (50 mL) (twice), and then dried with an air drier at 50°C to give 39.4 g (68.4%) of 2-methylene-4-(4-methylphenyl)-4-oxobutanoic acid (**2**). M.p.: 147–148°C (Lit.[1]: m.p.: 147–148°C). Additionally, ^{1}H-NMR spectra and IR spectra were identical with the reported data.[1]

Crude esonarimod (1). To a mixture of **2** (20.0 g, 97.9 mmol) and toluene (108 mL) –water (8.81 g, 489 mmol) was added thioacetic acid (**4**) (8.94 g, 117 mmol), and the mixture was heated to 60°C. A solution of Et_3N (1.98 g, 19.6 mmol) in toluene (13 mL) was then added dropwise over 30 min. The reaction mixture was stirred at 60°C for 240 min, and

then washed with 1.5 mol/L sulfuric acid (35 mL), water (35 mL, twice), and brine (35 mL). The extract was stirred at 0°C, and the precipitate was collected by the filtration and dried with an air drier at 50°C to give 24.4 g (89.0%) of crude **1**.

Esonarimod (1). A mixture of crude **1** (20.0 g, 71.3 mmol) and IPE (200 mL) was refluxed until it was dissolved. The mixture was cooled to −15°C and stirred for 30 min, and the precipitate was collected by filtration and dried with an air drier at 50°C to give 18.6 g (93.1%) of **1**. M.p.: 96–97°C (Lit.[1]: m.p.: 97°C). Additionally, ^{1}H-NMR spectra and IR spectra were identical with the reported data.[1]

Synthesis of 1 in a Pilot Plant

Aluminum chloride (50.0 kg, 375 mol) was added to nitrobenzene (131 kg) portionwise at 20°C over 10 min. Compound **3** (20.0 kg, 178 mol) was added, and 23.8 kg (258 mol) of toluene was then added dropwise over 30 min. The reaction mixture was stirred at 50°C for 120 min and then poured into conc. hydrochloric acid (43 kg) –water (143 kg) at 20°C over 120 min. Toluene (112 kg) was added and the mixture was stirred at −15°C for 60 min. The resulting precipitate was collected by centrifugation and washed with water (35 kg) and toluene (30 kg) to give 34.6 kg (wet) of **2**. The amount of **2** (dry) was 27.1 kg (74.2%), which was determined by drying a small amount of **2** (wet).

A sample of **2** (wet) (34.1 kg), which was equivalent to 26.7 kg (131 mol) of **2** (dry), was suspended in toluene (144 kg). Compound **4** (12.0 kg, 158 mol) was added and the reaction mixture was heated to 60°C. A solution of Et_3N (2.65 kg, 26.2 mol) in toluene (16.0 kg) was then added dropwise at 60°C. The reaction mixture was stirred at 60°C for 120 min, and washed with 1.5 mol/L of sulfuric acid (45 kg), water (45 kg), and brine (45 kg). Toluene (80.1 kg) was then added to the organic layer, and the mixture was stirred at −15°C for 60 min. The resulting precipitate was collected by centrifugation and dried with an air drier at 50°C to give 32.6 kg (88.9%) of crude **1**.

A sample of crude **1** (32.5 kg, 116 mol) was dissolved in IPE (325 kg) with heating. The extraneous material was filtered with a pressure filter, and the filtrate was stirred at −15°C for 60 min. The resulting precipitate was collected by centrifugation and dried with an air drier at 50°C to give 29.2 kg (89.8%) of **1**. M.p.: 96–97°C (Lit.[1]: m.p.: 97°C). Additionally, ^{1}H-NMR spectra and IR spectra were identical with the reported data.[1]

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