A Practical Procedure for the Synthesis of Esonarimod, (*R*,*S*)-2-Acetylthiomethyl-4-(4-methylphenyl)-4-oxobutanoic Acid, an Antirheumatic Agent (Part 1)

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An efficient and practical procedure for the synthesis of esonarimod, (*R*,*S*)-2-acetylthiomethyl-4-(4-methylphenyl)-4-oxobutanoic acid (1), a new antirheumatic drug, has been developed. The intermediate, 2-methylene-4-(4-methylphenyl)-4-oxobutanoic acid (2), was prepared by Friedel–Crafts acylation of toluene with itaconic anhydride (3) in the presence of aluminum trichloride and nitrobenzene in 63% yield without silica gel column purification. Compound 1 was prepared by Michael addition of 2 with thioacetic acid (4) in 74% yield. Overall, 1 was obtained in 47% yield from 3. The structures and synthetic mechanisms of by-products (five compounds) of 2 were also clarified.

Key words esonarimod; antirheumatic drug; Friedel–Crafts acylation; Michael addition; process chemistry

We originally developed esonarimod, (*R*,*S*)-2-acetylthiomethyl-4-(4-methylphenyl)-4-oxobutanoic acid (**1**), as a new antirheumatic drug.[1,2] Compound **1** has a variety of effects on cellular and mediator events in inflammatory processes, inhibits the production of inflammatory cytokines including interleukin-1, interleukin-6, and tumor necrosis factor-α from human peripheral blood mononuclear cells,[3] and suppresses the development of arthritis in various animal models.[1,2,4]

Our initial method for synthesizing **1** is outlined in Chart 1.[5,6]

In Step 1, 2-methylene-4-(4-methylphenyl)-4-oxobutanoic acid (**2**) is obtained by Friedel–Crafts acylation of toluene with commercially available itaconic anhydride (**3**) in the presence of aluminum trichloride. When dichloromethane or 1,2-dichloroethane was used as the solvent, **2** was obtained in 53% and 52% yield, respectively.[5,6] However, 1,2-dichloroethane is a Class 1 residual solvent, which should be avoided if possible in the manufacture of drug substances because of their unacceptable toxicity or their deleterious environmental effects.[7,8] Dichloromethane is also not an environmentally friendly solvent.[9] Finally the yield was not satisfactory.

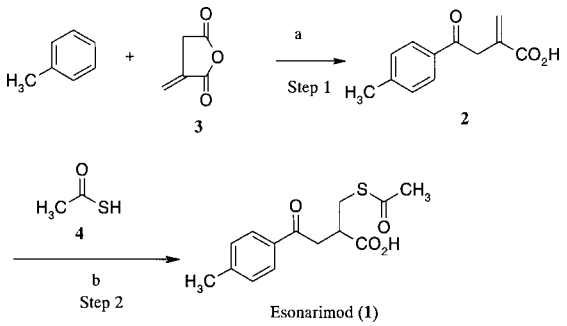
In Step 2, **1** was obtained in 73% yield by Michael addition of **2** with thioacetic acid (**4**). In the previous paper, potassium carbonate was used as the base for this reaction, and *N*,*N*-dimethylformamide and water were used as the solvent. Therefore, a large amount of solvent such as ethyl acetate was required for the extraction of **1**.

Since this initial synthetic method had several drawbacks from the standpoint of commercial production, as described above, a more efficient and practical procedure for the synthesis of **1** was required. We report here a process for the synthesis of **1**. We also discuss the structures of the by-products of the Friedel–Crafts reaction and the mechanism of their formation.

Results and Discussion

Synthesis of 2 (Step 1) A more appropriate solvent for the Friedel–Crafts reaction of toluene with **3** was investigated (Table 1).

When dichloromethane was used, **2** was obtained in 57% yield, along with small amounts of 3-methylene-4-(4-methylphenyl)-4-oxobutanoic acid (**5**), 6-methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid (**6**), 6-methyl-1-oxo-2,3-dihydro-1*H*-inden-2-ylacetic acid (**7**), 4-(4-methylphenyl)-2-[(4-methylphenyl)methyl]-4-oxobutanoic acid (**8**) and 2-methyl-4-(4-methylphenyl)-4-oxo-2-butenoic acid (**9**) (Entry 1). These compounds were separated by silica gel column chromatography, except for **6** and **7**, which were difficult to separate and obtained as a mixture. Consequently, the yields of **6** and **7** were determined by ^{1}H-NMR spectroscopy (δ 7.85, 7.58). The yield of **2** was slightly higher than reported previously.[5] Among the solvents tested, nitroethane gave the best yield (82%) with only small amounts of by-products, **5** and **9** (Entry 2). However, nitroethane is explosive.[10] Therefore, we next examined nitrobenzene, although nitrobenzene



(a) $AlCl_3$, CH_2Cl_2, rt, 53%; (b) K_2CO_3, DMF, H_2O, rt, 73%

Chart 1

Table 1. Solvent Effect for the Acylation of Toluene with Itaconic Anhydride (**3**)

Entry	Solvent	**2**	**5**	**6**	**7**	**8**	**9**
1	Dichlromethane	57%	5%	3%	2%	8%	0.2%
2	Nitroethane	82%	2%	—	—	—	1%
3	Nitrobenzene	70%	3%	0.4%	—	—	1%
4	Toluene	29%	—	12%	8%	8%	—

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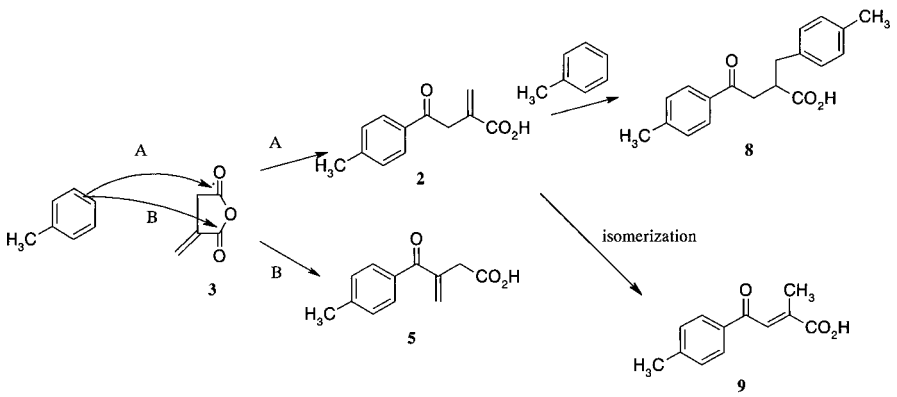
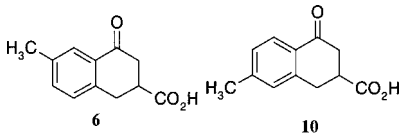


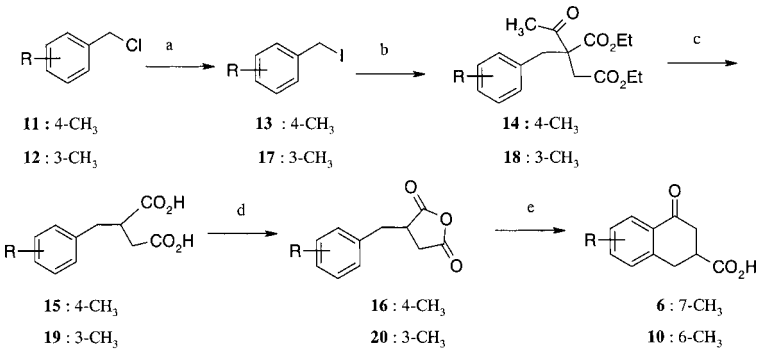
The Formation Mechanism of By-products **5**, **8**, and **9**

Chart 2



Strutures of **6** and **10**.

Chart 3



(a) NaI, acetone, rt; (b) diethyl acetylsuccinate, NaH, rt,; (c) NaOH, H_2O reflux; (d)Ac_2O, 110℃, (e) $AlCl_3$, nitrobenzene.

Chart 4

is highly toxic.[11,12] The reaction in nitrobenzene gave **2** in 70% yield (Entry 3). The use of toluene as the solvent reduced the yield of **2** and increased the formation of the undesired products **6**—**8** (Entry 4).

When the reaction of toluene with **3** was carried out in nitrobenzene using $AlCl_3$ followed by treatment with 3 mol/l hydrochloric acid and hexane, **2** was obtained in 63% yield as precipitates.

The Friedel–Crafts reaction of toluene with **3** produced byproducts such as **5**—**9**. Their structures are as shown in Table 1. The formation of these minor compounds **5**, **8**, and **9**, can be explained as follows (Chart 2).

Friedel–Crafts acylation of toluene with **3** (route A) produced **2**. The Michael addition of toluene to **2** formed **8**. On the other hand, **2** isomerized and gave **9**.[13,14]

The structure of **6** was initially assumed to be 7-methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid (**10**) formed by the intramolecular cyclization of **2**. However, treatment of **2** under these reaction conditions gave neither **6** nor **10**, and **2** was recovered unchanged (Chart 3).

To confirm the structure of **6**, we prepared **6** and the isomeric compound **10** by the unambiguous method[15] starting with 4-methylbenzylchloride (**11**) and 3-methylbenzylchloride (**12**), respectively (Chart 4). The reaction of diethyl 2-acetylsuccinate with **13** gave **14**, which was hydrolyzed to the acid (**15**) and then treated with acetic anhydride to give the anhydride (**16**). The intramolecular Friedel–Crafts acylation of **16** gave the desired **6**. In the same way, **10** was obtained from **12** *via* **17**—**20**.

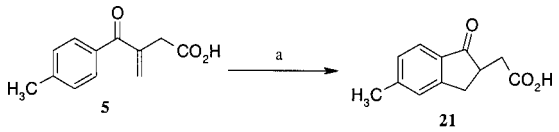
The ^{1}H-NMR spectrum of **6** obtained from the reaction mixture was completely identical to that of authentic sample (Table 2).[16]

Likewise, the structure of **7** was initially assumed to be 5-methyl-1-oxo-2,3-dihydro-1*H*-inden-2-ylacetic acid (**21**), which could be produced by the intramolecular acylation of **5**. Indeed, when **5** was treated under these reaction conditions, **21** was produced in 38% yield (Chart 5).

To confirm the structure of **7**, the authentic sample was

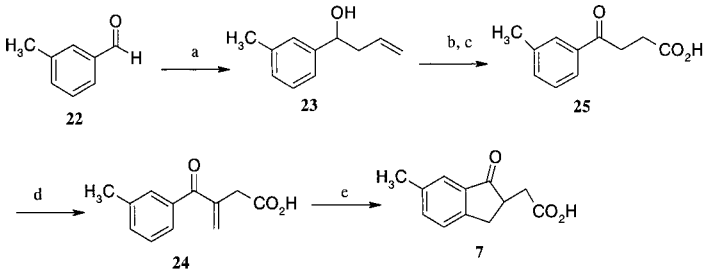
Table 2. ^{1}H-NMR Data of **6** Obtained from the Reaction Mixture, Authentic **6**, and Authentic **10** in $CDCl_3$

6 obtained from the reaction mixture	Authentic **6**	Authentic **10**
2.37 (3H, s)	2.37 (3H, s)	2.39 (3H, s)
2.75—3.02 (2H, m)	2.74—3.04 (2H, m)	2.73—3.03 (2H, m)
3.22 (3H, m)	3.12—3.32 (3H, m)	3.12—3.32 (3H, m)
7.18 (1H, d, *J*=8.0 Hz)	7.19 (1H, d, *J*=7.7 Hz)	7.10 (1H, s)
7.33 (1H, dd, *J*=2.0, 8.0 Hz)	7.34 (1H, dd, *J*=1.5, 7.7 Hz)	7.16 (1H, d, *J*=8.1 Hz)
7.85 (1H, d, *J*=2.0 Hz)	7.84 (1H, br s)	7.94 (1H, d, *J*=8.1 Hz)



(a) $AlCl_3$, nitrobenzene, 70 ℃, 3 h, 38%

Chart 5



(a) vinylmagnesium bromide, THF, rt, 1 h, 89%; (b) BH_3- THF, rt, 1 h ; (c) CrO_3 - H_2SO_4 , acetone, 40 min, 86%; (d) $(CH_2O)_n$, pyridine, 70- 75 ℃, 7.5 h, 50%; (e) $AlCl_3$,. nitrobenzene, 60℃, 2.5 h, 29%

Chart 6

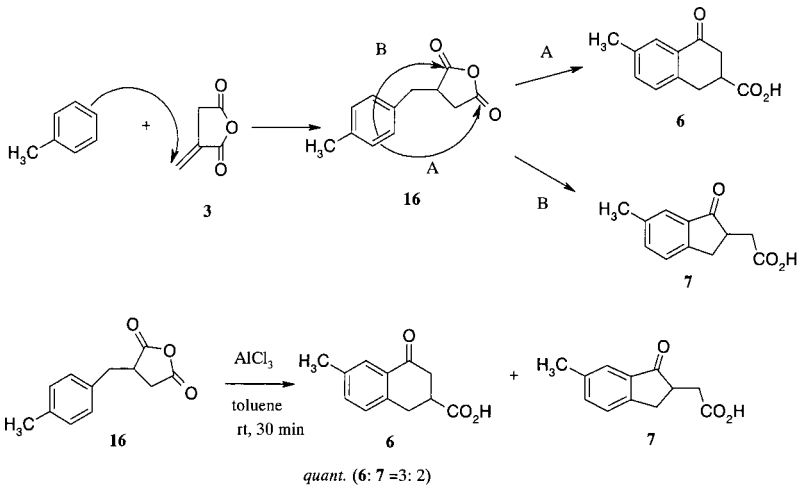
Table 3. ^{1}H-NMR Data of **7** Obtained from the Reaction Mixture, Authentic **7**, and Authentic **21** in $CDCl_3$

7 obtained from the reaction mixture	Authentic **7**	Authentic **21**
2.41 (3H, s)	2.41 (3H, s)	2.45 (3H, s)
2.64 (1H, dd, *J*=10.0, 17.0 Hz)	2.63 (1H, dd, *J*=9.6, 17.5 Hz)	2.61 (1H, dd, *J*=9.6, 18.0 Hz)
2.85 (1H, dd, *J*=4.0, 17.0 Hz)	2.85 (1H, dd, *J*=4.5, 17.0 Hz)	2.85 (1H, dd, *J*=4.3, 17.0 Hz)
2.95—3.12 (2H, m)	2.99—3.08 (1H, m)	2.98—3.07 (1H, m)
	3.04 (1H, dd, *J*=4.2, 17.5 Hz)	3.04 (1H, dd, *J*=4.5, 18.0 Hz)
3.43 (1H, dd, *J*=8.0, 17.0 Hz)	3.44 (1H, dd, *J*=7.8, 17.0 Hz)	3.43 (1H, dd, *J*=7.7, 17.0 Hz)
7.34 (1H, d, *J*=8.0 Hz)	7.36 (1H, d, *J*=7.8 Hz)	7.20 (1H, dd, *J*=0.5, 8.0 Hz)
7.44 (1H, d, *J*=8.0 Hz)	7.44 (1H, dd, *J*=1.2, 7.8 Hz)	7.26 (1H, d, *J*=0.5 Hz)
7.58 (1H, s)	7.58 (1H, d, *J*=1.2 Hz)	7.67 (1H, d, *J*=8.0 Hz)

prepared by the unambiguous route shown in Chart 6. The reaction of 3-methylbenzaldehyde (**22**) with vinylmagnesium bromide gave **23**, which was converted to **24** *via* **25** in 3 steps. Treatment of **24** with $AlCl_3$ in nitrobenzene afforded **7**. The ^{1}H-NMR spectrum of **7** obtained from the reaction mixture was completely identical to that of the authentic sample (Table 3).[16]

These results indicated that **2** and **5** were not the intermediates to **6** and **7**, respectively. A plausible mechanism for the formation of **6** and **7** is shown in Chart 7. Compound **16** would be a key intermediate to **6** and **7**, but has not yet been isolated. Fortunately, **16** was used as the intermediate for the authentic sample of **6**, as shown in Chart 4. Therefore, we treated **16** with $AlCl_3$ in nitrobenzene and obtained **6** in high yield (76%), but did not obtain **7**. On the other hand, the treatment of **16** with $AlCl_3$ in toluene at room temperature for 30 min gave 5- and 6-membered cyclization products **6** and **7** (the ratio was about 3 : 2) by the intramolecular acylation of both of the carbonyl group of **16**. This result supported the notion that **16** was a common intermediate to **6** and **7**.

Synthesis of Esonarimod (1) (Step 2) For the Michael addition of **2** with **4**, toluene was selected as the solvent and triethylamine as the base due to cost considerations. To prevent the isomerization of **2** to **9** by an excess of amine, the minimum amount of base required was examined. When 0.2 equivalents of triethylamine and 1.2 equivalents of **4** were used at 60 °C, the reaction was completed within 2 h.



The Plausible Mechanism of Formation of **6** and **7**

Chart 7

Table 4. Solvents for the Recrystallization of Esonarimod (**1**)

Entry	Solvent	Prurified **1**
1	1,4-Dioxane (5 ml)	27%
2	Acetone (5 ml)	47%
3	Ethyl acetate (5 ml)	68%
4	Methanol (5 ml)	54%
5	Ethanol (5 ml)	74%
6	IPA (5 ml)	71%
7	Toluene (5 ml)	91%
8	Toluene (20 ml)	84%
9	IPE (50 ml)	88%

All reactions were conducted on a 5.0 g scale. The purity of **1** was detected by HPLC. IPA: isopropyl alcohol, IPE: isopropyl ether.

We finally studied the purification of crude **1**. We examined the solvents for recrystallization, and the results are shown in Table 4.

Toluene was found to be a suitable solvent for the recrystallization of **1**. However, toluene then had to be removed. The residual toluene in **1** was over 1000 ppm. Toluene is a Class 2 residual solvent.[7,8] Therefore, we next selected isopropyl ether as the recrystallization solvent. The residual isopropyl ether was under 500 ppm, although the yield from **2** was 74%. Thus, **1** was obtained in the overall yield of 47% in 2 steps from **3**.

Conclusion

An efficient process for the large-scale synthesis of esonarimod (**1**) was established. Compound **1** was obtained in a higher overall yield than in the initial synthesis (47% from commercially available itaconic anhydride (**3**) *vs.* 39%).

In Step 1, some by-products, **5**—**9**, were found to be produced. The structures and the mechanism of the formation of these compounds were also clarified.

Experimental

General Melting points were determined by a Buchi 535 melting point apparatus and were uncorrected. IR 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. Elemental analyses were performed on a Perkin-Elmer 2400. TLC was performed on silica gel pre-coated plates (Merck, Kieselgel 60F254). Column chromatography was performed over silica gel (Wako, Wako gel C-200). 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. Gas chromatography was performed on a CBP20-S25-50 column (Shimadzu, 0.33 mm×25 m×0.50 μm) with flame ionization detector. $AlCl_3$, powder type, was purchased from Toyama Chemical.[17] Thioacetic acid (**4**) was purchased from Toyo Kasei Kogyo.[18]

3-Methylene-4-(4-methylphenyl)-4-oxobutanoic Acid (5), 6-Methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (6), 6-Methyl-1-oxo-2,3-dihydro-1*H*-inden-2-ylacetic Acid (7), 4-(4-Methylphenyl)-2-[(4-methylphenyl)-methyl]-4-oxobutanoic Acid (8) and 2-methyl-4-(4-methylphenyl)-4-oxo-2-butenoic Acid (9) A mixture of **3** (112 g, 999 mmol) and toluene (200 ml, 1.88 mol) was added dropwise to $AlCl_3$ (250 g, 1.87 mol)–dichloromethane (250 ml). The reaction mixture was stirred under ice cooling for 1 h, and then at room temperature for 6 h. The reaction mixture was poured into 3 mol/l hydrochloric acid, and the precipitate was collected by filtration. The crude product was recrystallized from ethyl acetate–hexane to give 106 g (52%) of **2**. This **2** included byproducts **5**—**9**, which were isolated by silica gel column chromatography.

5: mp 57—58 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.42 (3H, s), 3.56 (2H, s), 5.81 (1H, s), 6.02 (1H, s), 7.25 (2H, d, J=8.0 Hz), 7.47 (2H, d, J=8.0 Hz). IR (KBr) cm^{-1}: 3146, 1724, 1642, 1606, 1344. MS *m/z*: 205 $(MH)^+$. *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.43; H; 5.89.

6: mp 208—209 °C. ^{1}H-NMR was written in Table 2, IR (KBr) cm^{-1}: 2950, 1702, 1684, 1612. *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.32; H; 5.88.

7: mp 145—148 °C. ^{1}H-NMR was written in Table 3, IR (KBr) cm^{-1}: 2925, 1740, 1670, 1605. *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.63; H, 5.89.

8: mp 156—157 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.29 (3H, s), 2.41 (3H, s), 2.43 (1H, dd, J=4.6, 17.4 Hz), 2.56 (1H, dd, J=9.5, 14.0 Hz), 2.91 (1H, dd, J=9.5, 17.4 Hz), 3.04 (1H, dd, J=4.6, 14.0 Hz), 3.98—4.15 (1H, m), 7.02 (2H, d, J=8.1 Hz), 7.07 (2H, d, J=7.9 Hz), 7.26 (2H, d, J=7.9 Hz), 7.88 (2H, d, J=8.1 Hz). IR (KBr) cm^{-1}: 3020, 2926, 1706, 1664, 1604, 1436, 1342, 1012. MS *m/z*: 297 $(MH)^+$. *Anal.* Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.93; H, 6.61.

9: mp 140—141 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.18 (3H, d, J=1.5 Hz), 2.44 (3H, s), 7.31 (2H, d, J=8.1 Hz), 7.83 (1H, q, J=1.5 Hz), 7.89 (2H, d, J=8.1 Hz). IR (KBr) cm^{-1}: 2990, 2622, 1702, 1658, 1604, 1572, 1364. MS *m/z*: 205 $(MH)^+$. *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.57; H, 5.87.

Synthesis of 6-Methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (6). 4-Methylbenzyliodide (13) To a solution of 4-methylbenzylchloride (**11**) (11.5 g, 81.8 mmol) in acetone (115 ml) was added sodium iodide (13.5 g,

90.1 mmol). The mixture was stirred at room temperature for 3 h. Sodium iodide (1.00 g, 6.67 mmol) was added, the mixture was stirred for an additional 40 min. The reaction mixture was then diluted with water and extracted with hexane. The extract was washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to give 18.4 g (97%) of **13** as a yellow oil.

Diethyl 2-Acetyl-2-(4-methylphenyl)succinate (14) To a solution of diethyl acetylsuccinate (11.9 g, 55.0 mmol) in toluene (100 ml) was added 1.30 g (54.2 mmol) of sodium hydride oil suspension. Compound **13** (14.2 g, 61.2 mmol) was then added, an insoluble compound was produced immediately (probably sodium iodide). The reaction mixture was stirred at room temperature overnight, then acidified by aqueous hydrochloric acid and extracted with toluene. The extract was washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to give 23.3 g of **14** as a yellow oil.

2-(4-Methylphenyl)succinic Acid (15) To **14** (23.3 g, 72.7 mmol) was added a solution of sodium hydroxide (8.70 g, 218 mmol) in water (100 ml), and the mixture was refluxed for 17 h. Sodium hydroxide (1.50 g, 37.5 mmol) and water (10 ml) were added, and the mixture was refluxed for an additional 4 h. The reaction mixture was cooled, acidified with aqueous hydrochloric acid and extracted with ether. The extract was washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to afford a yellow oil. The residue was recrystallized from ethyl acetate–hexane to give 5.10 g (38% from **13**) of **15** as a white powder.

2-(4-Methylphenyl)succinic Anhydride (16) A mixture of **15** (2.22 g, 9.99 mmol) and acetic anhydride (10.2 g, 99.9 mmol) was heated to 110 °C. After stirring for 30 min, acetic anhydride was azeotroped with toluene to afford a pale yellow oil, which was recrystallized from hexane to give 1.86 g (91%) of **16**.

6-Methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (6) To a solution of **16** (1.84 g, 9.01 mmol) in nitrobenzene (5 ml) was added 2.52 g (18.9 mmol) of $AlCl_3$. The mixture was stirred at room temperature for 1 h, poured into aqueous hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and evaporated *in vacuo*. Nitrobenzene was azeotroped with water to give a white powder. The residue was dissolved in ethyl acetate, dried over $MgSO_4$, and concentrated to recrystallize. The crystal was filtered to give 1.40 g (76%) of **6**. mp 214—215 °C, ^{1}H-NMR was written in Table 2, IR (KBr) cm^{-1}: 2950, 1702, 1684, 1612, 1572, 1410. MS *m/z*: 205 $(MH)^+$. *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.49; H; 5.88.

Synthesis of 7-Methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (10). 3-Methylbenzyliodide (17) To a solution of 3-methylbenzylchloride (**12**) (11.1 g, 78.9 mmol) in acetone (111 ml) was added 23.7 g (158 mmol) of sodium iodide, and the mixture was stirred at room temperature overnight and then filtered. The solvent was evaporated *in vacuo*. The residue was diluted with water and extracted with ether. The extract was washed with water and aqueous sodium thiosulfate, dried over $MgSO_4$, and evaporated *in vacuo* to give 17.1 g (93%) of **17** as yellow oil.

Diethyl 2-Acetyl-2-(3-methylphenyl)succinate (18) To a solution of diethyl acetylsuccinate (15.4 g, 71.2 mmol) in toluene (100 ml) was added 1.70 g (70.8 mmol) of sodium hydride. Compound **17** (17.1 g, 73.7 mmol) was added, and an insoluble compound was produced immediately (probably sodium iodide). The reaction mixture was stirred overnight, acidified by aqueous hydrochloric acid and extracted with toluene. The extract was washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to give 22.2 g (94%) of **18** as yellow oil.

2-(3-Methylphenyl)succinic Acid (19) To **18** (22.2 g, 69.3 mmol) was added a solution of sodium hydroxide (8.30 g, 208 mmol) in water (100 ml). The reaction mixture was refluxed for 9 h and a solution of sodium hydroxide (1.40 g, 35.0 mmol) in water (6 ml) was then added. The reaction mixture was refluxed further overnight, cooled, acidified with aqueous hydrochloric acid and extracted with ether. The extract was washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to afford a brown oil. The residue was recrystallized from chloroform–hexane and then recrystallized again from acetone–hexane to give 7.90 g (52%) of **19** as a colorless powder.

2-(3-Methylphenyl)succinic Anhydride (20) A mixture of **19** (7.90 g, 35.5 mmol) and acetic anhydride (36.2 g, 355 mmol) was heated to 110 °C. After stirring for 30 min, acetic anhydride was azeotroped with toluene to afford a pale yellow oil, which was recrystallized from hexane to give 6.88 g (95%) of **20**.

7-Methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (10) To a solution of **20** (2.04 g, 9.99 mmol) in nitrobenzene (5 ml) was added 2.80 g (21.0 mmol) of $AlCl_3$. The reaction mixture was stirred at room temperature overnight, poured into aqueous hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and evaporated *in vacuo*. Nitrobenzene was azeotroped with water to afford a white powder. The residue was dissolved in ethyl acetate, dried over $MgSO_4$, and evaporated *in vacuo* to afford a pale yellow powder, which was washed with hexane and recrystallized from ethyl acetate to give 1.10 g (54%) of **10**. mp 196—197 °C, ^{1}H-NMR was written in Table 2, IR (KBr) cm^{-1}: 2974, 1700, 1678, 1608, 1438, 1262. MS *m/z*: 204 (M^+). *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.57; H; 5.83.

Synthesis of 6-Methyl-1-oxo-2,3-dihidro-1*H*-inden-2-ylacetic Acid (7). 1-(3-Methylphenyl)-3-buten-1-ol (23) To a solution of 3-methylbenzaldehyde (**22**) (4.00 g, 33.3 mmol) in tetrahydrofuran (50 ml) was added 50 ml of vinylmagnesium bromide (1 mol/l hexane solution) under ice cooling. The reaction mixture was stirred at room temperature for 1 h and then 1 mol/l hydrochloric acid (20 ml) was added. The mixture was then extracted with ethyl acetate, washed with brine and water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography using ethyl acetate : hexane = 1 : 3—1 : 1 to give 4.80 g (89%) of **23** as a colorless oil.

4-(3-Methylphenyl)-4-oxobutanoic Acid (25) To a solution of **23** (7.44 g, 45.9 mmol) in tetrahydrofuran (30 ml) was added 7.44 g of borane–tetrahydrofuran complex (1 mol/l). The reaction mixture was stirred at room temperature for 1 h and diluted with water (11.2 ml) and 3 mol/l sodium hydroxide (15 ml). Next, 30% hydrogen peroxide (15 ml) was added slowly, and the mixture was stirred at room temperature for 1 h. It was then diluted further with 150 ml of water and extracted with ethyl acetate. The extract was washed with brine, water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography using ethyl acetate : hexane = 2 : 3—1 : 0 to give 6.32 g (76%) of 1-(3-methylphenyl)-1,4-butanediol as a white crystal.

1-(3-Methylphenyl)-1,4-butanediol (6.00 g, 37.0 mmol) was dissolved in acetone (50 ml), and 4 mol/l Jones reagent (29 ml) was added. The reaction mixture was stirred at room temperature for 40 min and then diluted with water (100 ml) and extracted with ethyl acetate. The extract was washed with brine and dried over $MgSO_4$. It was evaporated *in vacuo*, and recrystallized from ethyl acetate to give 3.02 g of **25**. Its mother liquid was evaporated *in vacuo* and purified by column chromatography using ethyl acetate : hexane = 2 : 3—1 : 0 to give 2.47 g of **25**. Overall, 5.49 g (86%) of **25** was obtained.

6-Methyl-1-oxo-2,3-dihydro-1*H*-inden-2-ylacetic Acid (7) To a mixture of **25** (5.20 g, 27.1 mmol) and pyridine (22 ml) were added paraformaldehyde (2.70 g) and pyridine (0.45 ml) at room temperature. The mixture was stirred at 70 °C for 5 h, and then at 75 °C for 2.5 h. The reaction mixture was diluted with 1 mol/l hydrochloric acid (30 ml) and extracted with 200 ml of ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography using ethyl acetate : hexane = 2 : 3—1 : 0 to give 4.20 g of colorless crystals. Recrystallization from ether–hexane gave 2.74 g (50%) of 3-methylene-4-(3-methylphenyl)-4-oxobutanoic acid (**24**).

To a solution of **24** (1.95 g, 9.55 mmol) and nitrobenzene (15 ml) was added 2.80 g (21.0 mmol) of $AlCl_3$. The reaction mixture was stirred at 60 °C for 2.5 h, diluted with 2 mol/l hydrochloric acid (400 ml) and extracted with 200 ml of ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography using ethyl acetate : hexane = 1 : 2—2 : 1 to give 1.00 g of white crystals. Recrystallization from ethyl acetate–hexane gave 560 mg (29%) of **7** as colorless needles. mp 151—153 °C, ^{1}H-NMR was written in Table 3. IR (KBr) cm^{-1}: 2918, 1708, 1614, 1580, 1406, 1252. *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.44; H, 5.82.

Synthesis of 5-Methyl-1-oxo-2,3-dihydro-1*H*-inden-2-ylacetic Acid (21). 3-Methylene-4-(4-methylphenyl)-4-oxobutanoic Acid (5) To a mixture of succinic anhydride (15.0 g, 144 mmol) and toluene (91.5 ml, 859 mmol) was added 44.1 g (331 mmol) of $AlCl_3$, and the mixture was stirred at 50—60 °C for 2 h. It was then poured into 2.5 mol/l hydrochloric acid (250 ml), and the precipitate was collected by filtration. The precipitate was washed with 2.5 mol/l hydrochloric acid (100 ml), water (200 ml), and toluene (20 ml), recrystallized from ethyl acetate–hexane to give 24.0 g of 4-(4-methylphenyl)-4-oxobutanoic acid as colorless leaflets (1st crop). Its mother liquid was evaporated *in vacuo* and recrystallized from ethyl acetate–hexane to give 1.50 g of 2nd crop. Overall, 25.5 g (88%) of 4-(4-methylphenyl)-4-oxobutanoic acid was obtained.

To a mixture of 4-(4-methylphenyl)-4-oxobutanoic acid (10.0 g, 52.0 mmol) and pyridine (20 ml) were added paraformaldehyde (2.36 g) and pyridine (0.4 ml). The reaction mixture was stirred at 60 °C for 12 h, poured into 1 mol/l hydrochloric acid (300 ml) and extracted with 400 ml of ethyl acetate. The extract was washed with brine and water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography using ethyl acetate : hexane = 1 : 1—2 : 1 and recrystallized from ethyl ac-

etate–hexane to give 5.68 g of **5** as colorless crystals.

5-Methyl-1-oxo-2,3-dihydro-1*H*-inden-2-ylacetic Acid (21) To a mixture of **5** (5.20 g, 25.5 mmol) and nitrobenzene (39 ml) was added 7.48 g (56.1 mmol) of $AlCl_3$. The mixture was stirred at 70 °C for 3 h, poured into 1 mol/l hydrochloric acid (200 ml) and extracted with 300 ml of ethyl acetate. The extract was washed with brine and water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography using ethyl acetate : hexane = 1 : 1—1 : 0 and recrystallized from ethyl acetate–hexane to give 1.60 g of **21** as colorless crystals. From the mother liquid, 0.40 g of **21** was obtained. Overall, 2.00 g (38%) of **21** was obtained. mp 111—112 °C, ^{1}H-NMR was written in Table 3, IR (KBr) cm^{-1}: 3024, 2932, 1712, 1612, 1342, 1256. MS *m*/*z*: 204 (M^+). *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.51; H, 5.87.

Synthesis of Esobnarimod (1). 2-Methylene-4-(4-methylphenyl)-4-oxobutanoic Acid (2) One mole (134 g) of $AlCl_3$ was added portionwise to nitrobenzene (170 ml) at 25 °C and the mixture was stirred for 10 min. Compound **3** (56.0 g, 500 mmol) was then added, and 60 ml (563 mmol) of toluene was added dropwise over 10 min. The reaction mixture was stirred at 50 °C for 40 min, and then poured into conc. hydrochloric acid (100 ml)–water (400 ml) at 20 °C. Hexane (360 ml) was then added and the mixture was stirred for 20 min and filtered. The filtrate was washed with 3 mol/l hydrochloric acid (100 ml), water (100 ml) (twice), and IPE (100 ml) (twice) to give 64.3 g (63%) of **2**. mp 147—148 °C, ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.42 (3H, s), 3.97 (2H, s), 5.80 (1H, d, J=1.1 Hz), 6.52 (1H, d, J=1.1 Hz), 7.26 (2H, d, J=8.1 Hz), 8.35 (2H, d, J=8.1 Hz). IR (KBr) cm^{-1}: 1703, 1685, 1637, 1608, 1573, 1325, 1235, 809. MS *m*/*z*: 204 (M^+). *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.46; H, 5.87.

Esonarimod (1) To a mixture of **2** (64.3 g, 315 mmol) and 330 ml of toluene was added **4** (27.3 ml, 382 mmol), heated to 60 °C. A solution of triethylamine (9.1 ml, 65.3 mmol) in toluene (40 ml) was then added dropwise over 30 min. The reaction mixture was stirred at 60 °C for 4 h, diluted in 100 ml of ethyl acetate, and washed with 1.5 mol/l sulfuric acid (35 ml), water (35 ml) (twice), and brine (35 ml). The extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from 270 ml of isopropylether to give 65.3 g (74%) of **1**. The overall yield of **1** from **3** was 47%. mp 97 °C, ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.34 (3H, s), 2.41 (3H, s), 3.15—3.40 (4H, m), 3.46 (1H, m), 7.26 (2H, d, J=8.1 Hz), 7.85 (2H, d, J=8.1 Hz), 10.00 (1H, br s). IR (KBr) cm^{-1}: 1714, 1697, 1673, 1607, 1211, 816. MS *m*/*z*: 281 (MH^+). *Anal.* Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75; S, 11.44. Found: C, 59.77; H, 5.72; S, 11.45.

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